UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: March 20, 2014

SUBJECT: Thiophanate-Methyl and Carbendazim (MBC). Human Health Assessment Scoping Document in Support of Registration Review.

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Attached is the Health Effects Division's (HED) human health risk assessment scoping document for thiophanate-methyl and its metabolite, carbendazim, to support registration review.

Executive Summary

The Health Effects Division (HED) Thiophanate-Methyl/Carbendazim and the Antimicrobial Division (AD) Carbendazim Risk Assessment Teams have evaluated the database and the most recent human health risk assessments for the systemic benzimidazole fungicides, thiophanate-methyl (TM) and carbendazim (MBC). MBC is a pesticide active ingredient but is also a metabolite, environmental degradate and the pesticidally active moiety of TM. The two compounds are therefore considered together in this document. HED performed this evaluation in order to determine the scope of work necessary to support the established tolerances (for TM only) and existing registrations for both active ingredients. The primary sources of information were recent human health risk assessments written for TM (D330476, D330976 and D360951, 2009); the HED Chapter of the Reregistration Eligibility Decision (RED) document for TM (D275774, 2002); an updated hazard characterization for TM and MBC (D340134, 2007), and HED's revised residential exposure assessment for MBC in paint (D364554, 2009). Residue chemistry, dietary exposure and non-dietary exposure assessments, and toxicology evaluations were also considered.

The use patterns for these compounds are extensive, and for TM include food uses. Their pesticidal activity derives from inhibition of fungal β-tubulin polymerization.

Thiophanate-methyl: TM is registered for use on a variety of fruits, nuts, vegetables and field crops, commercial treatment of a variety of seeds including potato seed pieces and peanuts, greenhouses and nurseries (including bulb dip treatment). It is also registered for use on turf, which includes sod farms, golf courses, athletic and recreational fields, ornamental grasses for landscapes and interiorscapes. End-use products are formulated as liquids, granules (G), water dispersible granules (WDG), wettable powders (WP), water soluble bags (WSB) and dusts (for seed treatment). Products may be applied as a broadcast foliar or soil directed spray by ground, aerial, or hand held equipment, granular spreader, and commercial and on-farm seed treaters. The personal protective equipment (PPE) for applicators and other handlers consists of a range from baseline clothing (long-sleeved shirt, long pants, shoes plus socks) and chemical resistant gloves made of any waterproof material to the additional use of protective eyewear and an apron when mixing and loading.

The toxicology database for TM is largely complete for assessment of human health risk; however, additional toxicology data are required. Based on the potential for applicator inhalation exposure during spray application uses, a rat subchronic inhalation study is required. A developmental thyroid study is also required to assess potential thyroid effects in early development from exposure to TM.

The main target organ is the liver in the rat, dog and mouse. There is evidence that TM causes disruption of thyroid homeostasis in the rat and dog, secondary to liver toxicity. Other effects included decreased body weight/weight gain, mild red blood cell effects at higher exposures and, in rats, renal and testicular toxicity. In the rabbit, decreased food consumption was observed with dermal exposure.

Rat and rabbit developmental studies and a rat two-generation reproductive toxicity study showed no evidence of increased susceptibility. No reproductive toxicity was observed in the rat. Liver and thyroid were examined at week 8 for parental and F1 animals: effects were reported in both generations but at a lower incidence in the F1 offspring. TM did not show evidence of neurotoxicity, and a developmental neurotoxicity study is not required.

TM is classified as "likely to be carcinogenic to humans," based on thyroid tumors in rats and liver tumors in mice and evidence of aneugenicity, with a cancer potency factor (Q_1*) based on liver tumors in male mice.

In the most recent assessment (D360951; 6/24/2009), for chronic dietary and non-dietary (residential) exposure, the Food Quality Protection Act (FQPA) Safety Factor was reduced to a 3X due to a data gap for a developmental thyroid study. A 3X factor (as opposed to the default 10X) was deemed adequate for the following reasons: 1) the toxicology database is considered adequate to assess pre- and post-natal toxicity; 2) there was no evidence of increased susceptibity following in utero exposure to rat and rabbits and pre/post natal exposure to rats; 3) there was no concern for potential developmental neurotoxicity, and a developmental neurotoxicity study is not required; and 4) the point of departure used risk assessment would adequately address any potential for the concern for thyroid toxicity seen in the adult animals. For acute dietary risk assessment, the FQPA safety factor was removed (i.e., 1X) because developmental thyroid effects would not be expected to result from a single dose and would therefore not affect the point of departure selected for acute dietary risk assessment. The developmental thyroid assay will address the concern for any potential thyroid effects that might occur during late gestational and early postnatal development and therefore will not have an impact on the point of departure or the endpoint of concern used for acute dietary risk assessment.

HED has not revised the endpoints, doses, and safety factors for the purpose of this scoping assessment for registration review. However, to ensure that future human health risk assessments are consistent with science policies in place at the time of registration review and take into consideration any findings from the new studies, HED recommends reevaluation of: (1) endpoints selected for risk assessment and (2) reconsideration of the FQPA safety factor.

The residue chemistry database supporting the registered uses of TM is complete, and no new residue chemistry data are required. A revised dietary risk assessment will be conducted to include updated percent crop treated estimates, monitoring data if available, changes in toxicological endpoints, and revised estimated drinking water concentrations. The most recent drinking water assessments used modeling to estimate surface water and groundwater residues. The dietary exposure database is adequate to support the registration of TM. If the outstanding toxicity studies identify a more sensitive point of departure than any used in the most recent risk assessment, or if the points of departure are revised for any other reason, the revised values will be incorporated into the dietary risk assessment. Currently, the dietary (food and drinking water) risks are not of concern for the existing uses of TM.

The U.S. tolerance definition for TM differs from the Codex definition in that the Codex definition includes residues of the fungicide, benomyl. The structure of benomyl is similar to that of carbendazim. At one time, there were U.S. tolerances for benomyl, but these tolerances

have been cancelled. Benomyl is still used in other countries and, as a result, Codex Maximum Residue Levels (MRLs) are still in effect. During registration review, HED will revisit established tolerance levels and the tolerance definition and, where possible, harmonize them with Codex and Canadian MRLs and MRL definitions.

No new residential uses have been registered for TM since the RED (2005). Residential handler and post-application scenarios did not result in risks of concern. However, since the most recent residential assessment, guidance for assessing residential exposure has been revised by the 2012 Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessment, and updated cancer and non-cancer exposure and risk assessments will be needed. Furthermore, a rat subchronic inhalation exposure study is required. Since inhalation risks were previously assessed using an endpoint and dose from an oral study, revised residential handler exposure assessments (non-cancer) will be required under registration review to support use on residential turf, incorporating any new inhalation data as well as the 2012 SOPs.

An aggregate exposure assessment was performed for the 2005 TM RED document. This assessment combined exposure to TM and MBC and identified risks of concern for acute, short-term and chronic non-cancer and cancer aggregate exposure to TM and MBC. The most recent aggregate exposure assessment was conducted in 2009 for proposed new uses of TM. The 2009 assessment considered TM and MBC separately, rather than combining exposures to the 2 actives. Aggregate short- and intermediate-term and cancer risks for TM alone were not of concern. [HED notes that the proposed TM uses were not granted because they would have led to additional dietary exposure to MBC, for which residential risk estimates of concern were identified, and a safety finding could not be made under the FQPA]. A new aggregate assessment for TM will be required during registration review that includes current use patterns and incorporates any changes in endpoint selection, safety factors, and updated dietary and residential exposure estimates.

Occupational handler and post-application exposures were assessed in 2009 for proposed uses of TM on a variety of agricultural crops and non-crop land areas. The 2009 occupational assessment resulted in handler and post-application exposure risks of concern for multiple crops resulting from the use a variety of formulations and application methods, including commercial and on-farm seed treatment. However, the uses were not registered due to risk estimates of concern for MBC. During registration review, new occupational handler and post-application assessments will be conducted for existing uses as necessary, based on updated doses, endpoints, and procedures for dermal and inhalation risk assessment. The exposure database for TM is considered complete, and additional data are not required.

Carbendazim: MBC (methyl 1H-benzimidazol-2-ylcarbamate) is a systemic fungicide of the benzimadazole chemical class. Its pesticidal action derives from inhibition of fungal β-tubulin polymerization. MBC is also a metabolite of the fungicide TM in mammals and in the environment.

MBC antimicrobial registered products are formulated as in-can, ready-to-use and dry-film preservatives in adhesives (non-food), caulks, concrete, grouts, inks, paints, paper (non-food), plastic (including toys), roof coatings, sealants, stains, and textiles. Conventional use is for

seasonal suppression of fungus for ornamental trees, and the active is formulated as ready-to-use capsules applied via tree injection. The products registered for tree injection are intended for use by professional applicators only, including arborists.

The toxicology database for MBC is incomplete at this time. Under the revised 40 CFR Part 158 Guidelines (toxicology data requirements), an immunotoxicity study is required. An extended one-generation reproductive toxicity study is currently being conducted by the registrant to address the lack of an acceptable reproductive toxicity study, along with concern for evidence (quantitative and qualitative) of increased susceptibility in the offspring, the occurrence of malformations in fetuses following *in utero* exposures, and the need for additional data to better characterize potential neurodevelopmental effects observed in the pre-natal study with rats. During previous discussions with the Registrant on the study protocol, the Agency also requested that a cohort of animals be included to evaluate immunotoxicity parameters; this study could therefore also address the immunotoxicity study requirement.

The available toxicological data indicate the liver and testes are the major target organs for MBC-induced toxicity; the latter was observed following both oral and dermal exposure. Thyroid effects were not observed in the available studies, unlike TM. Olfactory degeneration of the nasal cavity and decreased body weight and weight gain were seen in a rat 90-day inhalation study conducted with the fungicide benomyl which is metabolized rapidly *in vivo* to MBC. No effects were reported at the exposure concentrations tested in a rat 5-day inhalation study on MBC.

Increased quantitative and qualitative susceptibility was observed in developmental toxicity studies with MBC in the rat and rabbit. Although developmental effects on the rat nervous system were reported, neurotoxicity is not observed in adult animals.

MBC was most recently classified as a Group C, or "possible human carcinogen" under the 1986 Agency cancer guidelines, based on liver tumors in female mice and aneugenic potential in genotoxicity studies. Cancer risk is assessed using a cancer potency (Q_1*) value.

HED has previously recommended retaining the 10X FQPA factor for all non-occupational exposure scenarios due to the lack of data on developmental neurotoxicity. The endpoints, doses, and safety factors used in the most recent updated exposure assessment for MBC (D364554, 2009) are considered appropriate based on the currently available data. To ensure that future human health risk assessments are consistent with science policies in place at the time of registration review and take into consideration any findings from new studies, HED recommends reevaluation of: (1) endpoints selected for risk assessment and (2) reconsideration of the FQPA safety factor.

There are no food/feed uses for MBC and therefore no residue chemistry data requirements. However, a dietary risk assessment is required because residues in drinking water are possible as a result of degradation of TM in the environment, and because residues of MBC are expected in food as a result of application of TM to crops. The most recent dietary assessment for MBC was conducted in 2012 (D397646) and did not identify risks of concern. However, during registration review, a new dietary risk assessment will be conducted incorporating the most

current pesticide residue monitoring data, drinking water and dietary models, along with any changes in endpoints, doses for risk assessment and safety factors.

Residential handler and post-application exposure may occur from antimicrobial uses of MBC (paint additive, treated items, tree injection). The most recent residential assessment was conducted in 2009 using the reduced concentration of MBC in paints and a revised dermal dose of 20 mg/kg/day. All paint handler scenarios resulted in MOEs (ranging from 34 to 87) below the LOC of 1000. A paint bioavailability study with MBC was submitted to refine the exposure estimates for residential painters, and the results of the study will be incorporated into a revised handler assessment for painters during registration review. Post-application exposure from the paint use is expected to be low, and will not be re-assessed during registration review. Handler exposure from tree injection use has not been assessed quantitatively in past risk assessments; however exposure is anticipated to be negligible. The tree injection product is formulated as ready-to-use, packaged in capsules which are inserted into a feeder tube which is dispensed into the tree. Therefore, the handler has no direct contact with MBC. No additional review of this scenario is needed during registration review. Post-application inhalation and dermal risks from exposure to MBC from treatment of turf with TM were not assessed because the exposures were considered to be negligible based on the reduction of the turf application rate in conjunction with the RED, and on the results of the chemical-specific turf transferable residue (TTR) study; during registration review, HED does not anticipate assessing post-application exposure to MBC as a result of TM use on turf.

Since the most recent residential assessment, guidance for assessing residential exposure has been revised by the 2012 Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessment. Therefore, during registration review, AD will conduct a new residential handler exposure assessment that will incorporate any new toxicological endpoints, points of departure and methods or policies for estimating exposure and risk associated with stain and paint products. In addition, AD anticipates conducting an exposure assessment for residential dermal and incidental oral post-application exposure for plastic toys and textiles.

For occupational and residential exposure, paint product use information is required (i.e., pouring liquid/solid material preservative formulation) to refine the daily amount handled; in addition, a description of the pouring operations should be submitted. Furthermore, for purposes of refining residential post-application exposure, chemical-specific indoor surface residue dissipation data and a description of human activity practices will be required for risk assessment purposes.

The most recent aggregate assessment for MBC was conducted in 2002 for the TM RED (D275774). During the course of evaluating proposed uses of TM in 2009, risk estimates of concern were identified for MBC for residential painters, based in part on new toxicology data. Once these risks were noted, HED did not conduct a full aggregate assessment for MBC including exposure from food and drinking water (from TM use). A new aggregate assessment will be conducted during registration review that includes current use patterns and incorporates any changes in scientific policy, new toxicology and residential exposure data, dose/endpoint selection and safety factors, as well as updated dietary exposure estimates.

Introduction

This document summarizes HED's and AD's evaluation of the data available for assessing human health risk from exposure to TM and MBC, as well as any data needed to support registration review. HED reviewed the conventional uses of both TM and MBC, while AD reviewed the antimicrobial uses of MBC [note: although HED evaluated the paint use in the 2009 assessment, during registration review the use pattern will fall under the purview of AD]. TM and MBC are systemic fungicides of the benzimidazole class, with a pesticidal mode of action of inhibition of tubulin formation in fungi. MBC is a metabolite of TM in mammals and a primary degradate identified in drinking water and residues of crops treated with TM. Both compounds are therefore being evaluated together in this scoping document, with each chemical discussed individually. The structures of TM and MBC may be found in the Chemical Identity Table (Attachment 1).

In conducting this evaluation, HED and AD have considered the most recent human health risk assessments, HED and OPPIN/PRISM databases, open literature (via Google Scholar) and the latest Agency science policies and risk assessment methodologies. HED and AD have evaluated this information for TM and MBC in association with the updates to their toxicity, exposure, and usage databases to determine if sufficient data are available and if further updates are needed to support registration review.

There are food and residential uses for TM. Products registered for use include dust (D), granular (G), wettable powder (WP), water-dispersible granular (WDG), flowable concentrate (FIC) and emulsifiable concentrate (EC) formulations. TM is currently registered for use on numerous fruit, vegetable, nut and field crops. Residential non-dietary exposure may occur from treatment of turf.

MBC is not registered for food uses at this time, but dietary exposure may occur due to contamination of drinking water as well as residues in food commodities due to applications of TM. It is currently registered for antimicrobial use patterns that may result in residential exposure. Registered products include in-can and dry-adhesive formulations for ornamental tree injection and as a preservative in various products that include non-food adhesives, caulks, concrete, grouts, inks, paints, paper, plastic, roof coatings, sealants, stains and textiles.

THIOPHANATE-METHYL

Hazard Identification/Toxicology

A summary of the available toxicity data on TM is provided in Attachment 3a. Since the previous human health risk assessment, conducted in 2009 (D330476), no additional toxicity studies have been submitted to the Agency. The database is largely complete, but under the revised 40 CFR Part 158 guidelines for toxicology data, a subchronic inhalation toxicity study in the rat is required based on the potential for inhalation exposure from numerous uses and portal of entry effects observed in a non-guideline inhalation study. A developmental thyroid study is also required to evaluate potential thyroid toxicity during early development based on thyroid effects in adult animals and residual uncertainties for the relative sensitivity of the young.

However, an immunotoxicity study is not required for TM, based on weight of evidence considerations (HASPOC memorandum, TXR# 0056916, U. Habiba, meeting of February 27, 2014; HASPOC Meeting memorandum, L. Hansen, 12/18/2008).

TM is of low or minimal acute oral and dermal toxicity (Categories III or IV) but of moderate acute inhalation toxicity (Category II). It is not irritating to the eye or skin (Category IV) and is a dermal sensitizer.

Metabolism data in the rat indicate that TM is well absorbed from the gastrointestinal tract, extensively metabolized and excreted primarily in the urine following a single low dose, but primarily via the feces following a single high dose, or following repeated dosing. Sixteen metabolites (12 identified) were observed with the major urinary metabolite being 5-hydroxy(2-methoxycarbonylamino) benzimidazolyl sulfate. MBC was also identified as a metabolite in both the urine and feces. Unchanged parent compound was identified with a single high dose or repeated low doses, primarily in the feces. Radioactivity was widely distributed but there was not significant accumulation, with the highest levels observed in the liver and thyroid. More than 90% of the administered radioactivity was excreted within 24 hours of dosing. The residues of concern for dietary exposure have been accounted for in the rat toxicity studies.

The liver is the major target organ for multiple species following oral exposure to TM. Hepatocellular hypertrophy and increased liver weight were observed in all species tested, along with effects on clinical chemistry parameters such as cholesterol, serum albumin, alkaline phosphatase and circulating thyroid hormones. Thyroid effects in rats, dogs and mice included enlargement, hypertrophy and follicular hyperplasia. Additional studies in the rat showed an increase in liver enzyme (UDPGT) activity along with effects on circulating thyroid hormones.

In addition to liver and thyroid effects, TM also caused mild red blood cell effects at the higher dose levels in rats, dogs and mice following subchronic or chronic exposure. In rats, TM caused toxicity to the kidney as indicated by increased urinary protein (in males), lipofuscin pigmentation, and increased severity of nephropathy following chronic administration. An increase in systemic calcification was observed in males and to a lesser extent in females and was probably secondary to hyperparathyroidism. Decreased body weight/weight gain was observed in both sexes. Effects on the testes were seen in rat chronic studies (one study showed decreased spermatogenesis; the other, testicular hyperplasia). Male rats appeared to be more sensitive than females overall based on greater severity of effects and high mortality at the highest dose tested (6000 ppm or 280.6 mg/kg/day, males and 334.7 mg/kg/day, females). Beagle dogs also showed decreased body weight. In the mouse carcinogenicity study, increased heart weight (females) and incidence of atrial thrombosis were observed.

TM is a carbamate, but only limited data are available on its potential to inhibit cholinesterase (ChE). As a class of compounds, thiocarbamates do not produce consistent cholinesterase inhibition patterns. In the rat subchronic toxicity study, serum cholinesterase activity was increased in males but decreased in females. In the rat chronic toxicity/ carcinogenicity study, males showed increases in serum ChE whereas at 24 months, it was decreased. ChE activity in females was slightly decreased at 6 and 12 months. RBC and brain ChE activities were not evaluated, and ChE was not measured in the subchronic or chronic dog studies.

Dermal exposure to TM for three weeks (5 applications per week) caused decreased food consumption in females and, at a higher dose, in males. Because this decrease was reported in both sexes and a dose-response was observed in females, it is considered treatment-related although no other signs of toxicity were observed. Comparison of the NOAEL/LOAEL of this study with those of oral studies provided an estimated dermal absorption value of 7%, based on maternal food consumption changes in the rat developmental toxicity study. Dermal irritation was observed at the site of application in all dose groups.

The only inhalation toxicity study submitted was a rat14-day inhalation toxicity study on a formulation containing 5.2% TM. Local pulmonary effects were observed at the LOAEL and decreased body weights at the HDT. In addition to testing a formulation and not the technical a.i., this study did not evaluate all of the standard parameters and therefore, was considered inadequate for assessment of inhalation toxicity for risk assessment purposes.

In the rat and rabbit developmental toxicity studies and the rat two-generation reproductive toxicity studies, there was no evidence of increased prenatal susceptibility. There was no evidence of reproductive toxicity in any of the studies. A limited evaluation of thyroid effects was performed on parental (P0) and first generation (F1) animals at 8 weeks of age in the two-generation reproductive toxicity study, along with assessment of several structural and functional developmental tests during lactation. Offspring had thyroid effects at comparable to parental animals but at lower incidence. There were no treatment-related effects on the developmental tests. The data did not indicate increased developmental susceptibility; however, an examination of offspring thyroid function during late gestation/lactation and/or early post-weaning times was not performed.

TM did not show evidence of neurotoxicity. Transient tremors following capsule dosing were observed in the first weeks of the chronic dog study, but at dose levels that caused significant toxicity and were not seen at later times, and were not observed in the subchronic dog study. In the rat acute neurotoxicity study, decreased landing foot splay at the time of peak effect was observed, but not at later times or in the subchronic neurotoxicity study, and did not show a dose-response. These findings were therefore not considered indicative of neurotoxicity. A developmental neurotoxicity study is not required.

In the most recent assessment (D360951**;** 6/24/2009), for chronic dietary and non-dietary (residential) exposure, the Food Quality Protection Act (FQPA) Safety Factor was reduced to a 3X due to a data gap for a developmental thyroid study. A 3X factor (as opposed to the default 10X) was deemed adequate for the following reasons: 1) the toxicology database is considered adequate to assess pre- and post-natal toxicity; 2) there was no evidence of increased susceptibility following *in utero* exposure to rat and rabbits and pre/post natal exposure to rats; 3) there was no concern for potential developmental neurotoxicity, and a developmental neurotoxicity study is not required; and 4) the point of departure used risk assessment would adequately address any potential for the concern for thyroid toxicity seen in the adult animals. For acute dietary risk assessment, the FQPA safety factor was removed (i.e., 1X) because developmental thyroid effects would not be expected to result from a single dose and the additional data would not affect the point of departure selected for acute dietary risk assessment.

The developmental thyroid assay will address the concern for any potential thyroid effects that might occur during late gestational and early postnatal development and therefore will not have an impact on the point of departure or the endpoint of concern used for acute dietary risk assessment.

TM is classified as "likely to be carcinogenic to humans" under the Agency's final guidelines for carcinogenicity assessment (2005), based on an increased incidence of liver tumors in mice and thyroid follicular cell adenomas/carcinomas in rats. Although there is evidence of antithyroid activity via increased hepatic UDP-glucuronosyltransferase (UDPGT) activity, the data to support a threshold antithyroid mode of action for thyroid tumors was considered inconclusive. The available genotoxicity data indicate aneugenic potential; therefore, a default quantification of cancer risk was performed using linear-low dose extrapolation based on the incidence of liver tumors in male mice, with a cancer potency factor, Q_1*, of 1.16×10^{-2} $(mg/kg/day)^{-1}$.

Endpoints selected for the most recent human health risk assessment (2009) are shown in Attachment 2a. An acute dietary assessment is required only for females 13-49 years of age based on developmental effects, because an appropriate single-dose endpoint was not identified for the general population. Non-dietary residential endpoints are required because there are turf uses of TM that may result in short- and intermediate-term handler or post-application dermal and inhalation exposure, as well as incidental oral exposure. HED will reevaluate endpoints and uncertainty factors (UFs) for risk assessment during registration review, taking into consideration the results of any new studies and current science policies at the time of the review.

Conclusions for Hazard Identification/Toxicology of TM

Additional toxicology data are required for TM, based on the recently revised data requirements for food use pesticides in 40 CFR Part 158. A subchronic toxicity study in the rat (870.3465) is required to support registration review, based on the potential for significant inhalation exposure for occupational uses of TM and evidence for potential portal of entry effects. In addition, a developmental thyroid study is required to evaluate potential secondary effects of thyroid hormone alteration during late pre-natal and early post-natal development. An immunotoxicity study is not required, based on lack of evidence of potential immunotoxicity at relevant dose levels.

During registration review, HED recommends reevaluation of the following points, which should take into consideration the results of the additional data studies received for TM and ensure consistency with science policies in effect at the time of review: (1) endpoints for risk assessment and (2) reconsideration of safety/uncertainty factors, including the FQPA safety factor.

Dietary Exposure

The residue chemistry database is adequate to support current registration review data requirements (D308747, 3/19/2009; D335849, 5/12/2009). The 2002 residue chemistry chapter of the RED cited numerous data deficiencies for the analytical methods and field trial studies.

The registrant submitted data in response to the cited deficiencies, and HED concluded the data were adequate.

Tolerances for TM have been established for numerous crops. In plant and livestock commodities, the residues of concern for tolerance enforcement are TM and MBC, calculated as the stoichiometric equivalent of TM. For risk assessment, the residues of concern in plants are TM, MBC, and the metabolite 2-AB. In livestock commodities, the residues of concern are TM, MBC, and the metabolites 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S. The degradates of concern in drinking water are TM and MBC only.

In 2009, HED performed a human health risk assessment for proposed uses of TM on numerous commodities (D330467). Although there were no aggregate risk estimates of concern for TM alone, there were residential exposure estimates of concern for MBC and, therefore, the proposed uses were not granted. In support of the 2009 assessment, HED conducted acute, chronic, and cancer dietary exposure assessments. A partially refined acute probabilistic dietary exposure analysis was performed for the population subgroup females 13-49 only, and was based on field trial and residue monitoring data [Pesticide Data Program (PDP) monitoring data]; percent crop treated estimates for many commodities, and a modeled drinking water estimate. Acute exposure and risk for females 13-49 years old were not of concern to HED (8.6% acute Population Adjusted Dose, or aPAD). A refined chronic dietary analysis was also conducted for this assessment in order to address both the non-cancer and cancer risk assessments. The chronic analysis included residue refinements from field trials and PDP, percent crop treated and projected percent crop treated estimates, and modeled drinking water estimates. The resulting chronic dietary risk estimate for Children 1-2 years old, the most highly exposed population subgroup, was not of concern at 3.6% chronic Population Adjusted Dose (cPAD). The cancer risk estimate was 4.7×10^{-6}. However, when the proposed use on citrus was excluded, the cancer risk estimate decreased to 3.3×10^{-6}.

The Environmental Fate and Effects Division (EFED) recommended that modeled estimates of residues in drinking water be used in the most recent dietary risk assessment. EFED is requesting updated environmental fate studies because the submitted studies do not meet current standards. These studies indicate that five degradates might be of concern if they are found to be major degradates. HED's Residues of Concern Knowledgebase Subcommittee (ROCKS) has determined that these degradates would probably be considered to be of equal toxicity to the parent compounds. Once the updated studies are received and reviewed, HED and EFED will determine whether or not the additional degradates are of concern. As a result, it's likely that HED and EFED will determine that an updated drinking water assessment is needed, and if this is the case, the results will be included in HED's preliminary risk assessment to support registration review. A new dietary assessment will include the most recent consumption data and the most current version of the dietary exposure model.

Conclusions for Dietary Exposure

The dietary exposure database is adequate to support the existing registrations and tolerances. No new residue chemistry data are required. However, a new dietary risk assessment will be conducted during registration review to include updated percent crop treated estimates, residue

monitoring data if available, changes in toxicological endpoints, updated consumption data, and the revised estimated drinking water concentrations.

Residential Exposure

Handler Exposure

TM is registered for use on residential turf, golf courses, athletic and recreational fields, ornamental grasses, and landscapes. The products registered for residential use are formulated as liquids, granules (G), water dispersible granules (WDG), wettable powders (WP) and water soluble bags (WSP) and may be applied by a variety of hand held equipment and granular spreaders.

The primary source of information used to evaluate residential handler exposure was the HED Human Health Risk Assessment for the RED (D275774, 2002). Although a revised residential assessment was performed in 2009, the residential handler section was based on the 2002 RED assessment. The TM RED assessed short-term residential non-cancer and cancer handler dermal and inhalation exposure resulting from use of hand held equipment (i.e., hose-end, back-pack, and manually pressurized handwand sprayers) for liquid formulations on ornamental plants (i.e. including backyard orchards) and push-type spreader for granular formulations on lawns. Furthermore, in order to mitigate handler risks identified in the assessment, the principal Registrants agreed to remove the use of hand or belly grinder applications from the labels of products that may be purchased by residents. The Registrants also agreed to restrict the use of ready-to-use liquids to spraying of ornamentals. The RED also indicates that there is a WP formulation for use on turf and ornamentals; however, it is not intended for residential use and was therefore considered unlikely to be sold to the general public and was not evaluated. Since there are concerns that such label language is not legally enforceable (unless the active ingredient is considered to be a restricted use pesticide), HED typically assesses potential exposure to residential users in the event that they are able to purchase and apply the product. Since TM is not restricted use, HED will conduct a handler assessment for the wettable powder on turf and ornamentals during registration review. Short-term risk estimates for residential handlers did not exceed HED's level of concern (LOC = margins of exposure (MOEs) > 300) for any scenario. Handler total MOEs ranged from 1,900 to 35,000. Cancer risk estimates were less than 10^{-7} for all scenarios.

No new or additional residential uses have been registered for TM since the 2005 RED. However, since the most recent residential assessment, guidance for assessing residential exposure has been revised by the 2012 Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessment. Furthermore, in accordance with the Part 158 Data Requirements for conventional pesticide active ingredients a 28-day inhalation exposure study is now required. Since inhalation risks were assessed using the endpoint and dose from an oral study, a revised residential handler exposure assessment (non-cancer and cancer) will be required under registration review for all formulations of products used on residential turf. This assessment will incorporate the additional TM inhalation toxicology studies, updated human exposure factors assumptions (e.g., body weight), and the 2012 SOPs for Residential Pesticide Exposure Assessments.

TM Post-application Exposure

The primary source of information used to evaluate residential dermal post-application exposure and risk resulting from the use of TM on turf was the 2009 assessment entitled "Revised Residential Exposure Assessment for Use of TM on Turf" (D360623, 2009). In the revised version, HED reassessed the 2002 residential turf exposure assessment (Revised TM Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document (RED), D279269, 2009) to reflect a reanalysis of the dermal and oral post-application exposure and risk resulting from use on turf. In accordance with the updated Part 158 data requirements (2007), a turf transferable residue (TTR) study for occupational (e.g., sod farms, golf courses, parks and recreational areas) or residential turf uses was submitted for TM (Dissipation of transferable turf residues of 3336WP 50 percent TM, MRID 45000701). HED averaged the daily predicted chemical-specific TTR values over 14 days which is in accordance with the minimum retreatment interval specified on the product labels to determine non-cancer dermal post-application exposure and risk. All adult and children residential lawn and golf dermal scenarios resulted in risk estimates which were not of concern. All incidental oral scenarios resulted in risk estimates greater than the LOC and therefore posed no risk of concern. To determine residential post-application cancer risk to homeowners and golfers exposed to treated turf, HED used a draft approach to estimate a range of available residues based on retreatment intervals of 14 days in combination with a range of possible number of applications per year and a chemical specific TTR study to better refine cancer risk. HED's calculations indicated residential post-application cancer risk resulting from exposure to turf ranged from 4.5×10^{-8} to 3.2×10^{-7} for 5 applications.

Since the most recent residential assessment, guidance for assessing residential exposure has been revised by the 2012 Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessment. Therefore, a revised residential post-application exposure and risk assessment (non-cancer and cancer) for turf will be required during registration review for all formulations of products used on commercial and residential treated turf.

Spray Drift and Volatilization

Residential exposures resulting from off-site transport (e.g., spray drift or volatilization) may occur as a result of applications of TM. The Agency is in the process of evaluating these types of exposures and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate these post-application exposures into the Agency's risk assessments. The need for spray drift and volatilization risk assessments for TM will be examined during Registration Review.

Conclusions for Residential Exposure

No new or additional residential uses have been registered for TM since the 2005 RED. Furthermore, no additional data are required at this time. Therefore, the residential exposure database is adequate to support the registration review process for TM. However, since the most recent residential assessment, guidance for assessing residential exposure has been revised by the 2012 Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessment.

Therefore, revised residential handler and post-application exposure and risk assessments (non-cancer and cancer) will be required during registration review for all formulations of products used on commercially treated and residential turf. This assessment should incorporate, as necessary, the additional TM inhalation toxicology study, updated human exposure factors assumptions (e.g., body weight) and the 2012 SOPs for Residential Pesticide Exposure Assessments.

Aggregate Risk Assessment

In accordance with the FQPA requirements for food use chemicals, when there are potential residential exposures to a pesticide, an aggregate risk assessment must consider exposure from three major routes: oral, dermal, and inhalation. There are three sources for these types of exposures: food, drinking water, and residential uses. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a no-observed-adverse-effect-level, NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposure and risk from various sources, HED considers both the route and duration of exposure. In the most recent risk assessment, HED provided updated aggregate exposure and risk estimates (D330476, 2009). The aggregate risk assessments that were performed were for acute, short- and intermediate-term, chronic and cancer risk scenarios for adults and children.

Dietary (food and water) consumption is the only source of exposure to TM that is expected to result in acute exposure. Therefore, the acute aggregate exposure and risk estimates are equivalent to the acute dietary exposure and risk estimate discussed above and were not of concern. The exposures resulting from short- and intermediate-term residential uses must be aggregated with the dietary (food and water) exposures. Short- and intermediate-term aggregate risk estimates for adults and children were not of concern.

Both cancer and non-cancer aggregate risk estimates were conducted. Non-cancer chronic aggregate risk is equivalent to non-cancer dietary exposure from food and drinking water, which was not of concern for TM as discussed above.

A cancer aggregate risk assessment was performed for the general U.S. population. Aggregate cancer risk is comprised of the risk from dietary sources (food and drinking water) and the risk from residential handler and post-application uses on lawns and golf courses. The aggregate cancer risks were all in the range of 10^{-6} or below.

Conclusions for Aggregate Assessment

HED anticipates that a new aggregate assessment will be required for TM during registration review. Additional toxicology data on TM may change the endpoints selected for risk assessment, and could impact the selection of safety and uncertainty factors. Because of updated science policies, new residential and dietary exposure estimates will result in the need for new aggregate exposure and risk assessments.

Occupational Exposure

Occupational Handler Exposure

TM is registered for use on a variety of fruits, nuts, vegetables and field crops, treatment of a variety of seeds (e.g., cotton, corn, vegetables, soybean, wheat and sunflower) including potato seed pieces and peanuts, greenhouses and nurseries (including bulb dip treatment). It is also registered for use on turf, which includes sod farms, golf courses, athletic and recreational fields, and ornamental grasses for landscapes and interiorscapes.

TM end-use products for occupational use are formulated as liquids, granules (G), water dispersible granules (WDG), wettable powders (WP), water soluble packets (WSP), and dust for seed treatment. Products may be applied as a broadcast foliar or soil directed spray by ground, aerial, by hand held equipment, and granular spreaders or commercial or on-farm seed treaters. The PPE for applicators and other handlers consists of a range from baseline clothing (long-sleeved shirt, long pants, shoes plus socks) and chemical resistant gloves made of any waterproof material to the additional use of protective eyewear and apron when mixing and loading.

The primary source of information used to evaluate occupational handler exposure, including commercial and on-farm seed treatment, was from the most recent occupational exposure assessment written for this chemical (D335120, 2009). However, this document did not include a revised commercial handler assessment for turf uses. Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of TM, HED used surrogate data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 (PHED Surrogate Exposure Guide, 8/98) to assess exposures for crop protection uses. Standard assumptions established by the HED Science Advisory Council for Exposure were used for acres treated per day and body weight. For seed treatment uses, handler assessments were based on the unit exposure data from the Science Advisory Council for Exposure (Exposure SAC) Policy #14: Standard Operating Procedures (SOP) for Seed Treatment (May 1, 2003) and on the treating/planting data from the Exposure SAC Policy #15: Amount of Seed Treated or Planted Per Day (March 2, 2004).
Risks of concern were identified for non-cancer handlers mixing/loading wettable powder, dry flowable and liquid formulations for aerial, chemigation, ground boom and airblast applications for a variety of proposed uses, which weren't registered due to risk estimates of concern identified for MBC. Since the most recent occupational exposure assessment, the standard values recommended for use in predicting handler exposure, known as "unit exposures," have been updated in the new "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[i]"; in addition, standard body weights for determining risk estimates have been updated. Furthermore, HED is in the process of revising seed treatment Policies 14 and 15 with updated inputs and assumptions from additional seed treatment studies and survey information. Therefore, an updated non-cancer and cancer occupational handler exposure assessment will be required for registered agricultural, seed treatment, and commercial turf (i.e. golf course maintenance) uses during registration review.

[i] **Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf**

TM Occupational Post-application Exposure

As indicated previously, a quantitative dermal post-application exposure assessment was most recently performed in 2009. The estimations of post-application exposures were based on the chemical specific dislodgeable foliar residue (DFR) data obtained from three studies: (1) an apple DFR study (MRID 44876301), (2) a strawberry DFR study (MRID 44866201), and (3) a grape DFR Study (MRID 46388701). Therefore, no additional data are needed at this time. Non-cancer dermal post-application exposure estimates were assessed based on predicted DFR data on day 0 (day of application), and risks of concern were identified for certain activities in a number of crops. Cancer dermal post-application exposure was assessed based on average DFR data in the range of day 1 to day 14, since TM labels permit reapplication at 14-day intervals. The dermal cancer risk estimates ranged from $1.6 \times 10^{-5} \sim 1.5 \times 10^{-7}$. It should again be noted that a post-application exposure assessment for commercial turf (i.e., golf course maintenance) use was not included in the 2009 assessment, since it was not a new use under consideration.

A quantitative post-application inhalation exposure assessment was not performed for TM based on the Agency's current practices. However, there are potential sources of inhalation exposure to workers performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and re-suspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (*http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html*). The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the Agricultural Reentry Task Force and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for TM.

Since the 2009 assessment, HED has revised various transfer coefficients within the Outdoor Residential Exposure Task Force (ORETF) and the Agricultural Re-entry Task Force (ARTF) databases, with data from new exposure monitoring studies. Therefore, updated non-cancer and cancer occupational post-application exposure assessments will be required for registered agricultural and commercial turf uses during registration review.

Conclusions for Occupational Exposure

The occupational exposure database for TM is complete and no additional data are needed at this time. However, since the most recent occupational exposure assessment, the standard values recommended for use in predicting handler exposure, known as "unit exposures," have been updated in the new "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[ii], and updated body weight assumptions are typically used for determining risk estimates. Furthermore, HED is in the process of revising seed treatment Policies 14 and 15 with updated inputs and assumptions from additional seed treatment studies and survey information.

[ii] **Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf**

Therefore, updated non-cancer and cancer occupational handler exposure assessments will be required for agricultural, seed treatment, and commercial turf uses during registration review. Furthermore, HED has revised various transfer coefficients within the Outdoor Residential Exposure Task Force (ORETF) and the Agricultural Re-entry Task Force (ARTF) databases. Therefore, updated non-cancer and cancer occupational post-application exposure assessments will be required for agricultural and commercial turf uses during registration review. HED will also consider the impact of new policies and procedures, such as addressing volatilization exposure, as well as the potential for exposure from spray drift during registration review.

Tolerance Assessment and International Harmonization

Tolerances for residues of TM in or on agricultural commodities are established in 40CFR §180.371. For plant commodities, the tolerances are established as follows: "Tolerances are established for residues of TM, dimethyl((1,2-phenylene) bis (iminocarbono-thioyl)) bis (carbamate), including its metabolites and degradates, in or on the commodities in the following table. Compliance with the tolerance levels specified in this paragraph is to be determined by measuring only the sum of TM, dimethyl((1,2-phenylene) bis (iminocarbono-thioyl)) bis (carbamate), and its metabolite, methyl 2-benzimidazoyl carbamate (MBC), calculated as the stoichiometric equivalent of TM, in or on the commodity."

Maximum residue limits (MRLs) for residues of TM have been established by Codex and Canada, but not by Mexico. The Codex MRLs are expressed in terms of the sum of benomyl, MBC, and TM, expressed as MBC, and are, therefore, not compatible with U.S. tolerances. Codex MRLs range from 0.05 ppm for wheat grain to 5 ppm for head lettuce. As with the U.S. tolerances, the Canadian MRLs are established based on residues of MBC and TM; however, in Canada, MRLs are expressed as MBC, rather than TM. Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes.

All benomyl uses have been cancelled in the U.S. As a result, the U.S. tolerance definition for TM differs from the Codex MRL definition. Although the U.S. tolerances and Canadian MRLs include the same two compounds, the MRLs are not expressed in terms of the same compound. During registration review, HED will revisit the tolerances and tolerance definitions, and harmonize them with the Codex and Canadian MRLs and MRL definitions, when possible. The international residue limit status sheet can be found in Attachment 5.

Data Requirements

The following toxicology studies are required for TM:

870.3465 Subchronic inhalation study in the rat. This study is required to assess occupational and residential handler inhalation exposure, based on high application rates and potential inhalation exposure during spray application uses, and evidence of portal of entry effects in a 14-day inhalation study on a 5% TM formulation.

Developmental thyroid study in the rat. This study is required to evaluate potential developmental effects from perturbation of thyroid levels.

No new residue chemistry, residential or occupational exposure data requirements have been identified for TM to support registration review.

MBC

Hazard Identification/Toxicology

The toxicology database for MBC is not complete for assessment of human health risk. There are currently data gaps for an immunotoxicity study (870.7800), a rat two-generation reproductive toxicity study (870.3800) and a rat developmental neurotoxicity study (870.6300). However, an extended one-generation reproductive toxicity study is currently in progress in response to the data requirements in the RED, which may satisfy the requirement for these studies. Additionally, the Agency requested during review of this study protocol that a cohort for immunotoxicity should be included which may satisfy the gap for the immunotoxicity study. A 21/28-day dermal toxicity study in the rat has been submitted (MRID 47341601) since the previous assessment and satisfies the requirement from the post-RED DCI of January 4, 2005. In the rat, MBC has been shown to be rapidly absorbed and extensively metabolized. Urine is the primary route of excretion at lower doses, but at higher doses it becomes saturated and accounts for only 41% of the excretion. Distribution of MBC or its metabolites to tissues is limited and radioactivity was not retained (less than 1% was detected in the liver and carcass). The primary routes of metabolism involved oxidation of the phenyl ring followed by sulfate or glucuronide conjugation of 5-hydroxyMBC and 5,6-dihydroxyMBC. Phenyl ring oxidation and N-oxidation at the imidazole N were also observed, especially in female rats.

MBC is of low to minimal acute toxicity (Category III - IV) by all routes. It is minimally irritating to the eye (III), slightly irritating to the skin (IV), and is not a dermal sensitizer. It does not cause delayed neurotoxicity in the hen.

Liver and testes are the major target organs of MBC toxicity. The mammalian mechanism of toxicity of MBC has not been fully characterized, although some effects such as aneuploidy and testicular toxicity may be derived from its ability to disrupt tubulin polymerization. Liver effects include cirrhosis, swelling and necrosis, and changes in alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT), albumin and cholesterol levels in plasma. Unlike TM, thyroid effects have not been reported.

Testicular degeneration was observed in subchronic and chronic dog studies, although not in the subchronic and chronic rat studies. Guideline reproductive toxicity data are not available at this time, but other studies indicate adverse reproductive effects on the testes in the rat (premature release of immature germ cells, slight atrophy of seminiferous tubules). Seminiferous tubule degeneration and hypospermia were reported in the rat following a 28-day dermal treatment at 720 mg/kg/day, with a NOAEL of 20 mg/kg/day. Because of the large dose spacing, a benchmark dose, lower confidence limit 10% ($BMDL_{10}$) of 68 mg/kg/day was calculated for short-term exposure, which may be used for short-term exposure. A dermal absorption factor of 3.5% was determined using data obtained from benomyl, now a cancelled pesticide, which

metabolizes *in vivo* to MBC; this factor was used to assess cancer risk associated with dermal exposure.

A 90-day inhalation study in the rat on benomyl showed olfactory degeneration of the nasal cavity and, at higher doses, decreased body weight and weight gain in males. No effects were reported in the rat following five days of exposure to MBC via nose-only inhalation exposure.

Increased susceptibility of offspring is observed in developmental toxicity studies. In the rat, fetuses showed skeletal variations associated with delayed growth. At doses below maternally toxic levels, fetuses showed decreased body weight and an increase in skeletal variations (bipartite ossification, dumbbelled vertebral centra). Because some of the malformations reported at the high dose were seen at the developmental LOAEL and not in control or low dose animals, it was considered a possible threshold level for developmental malformations. At maternally toxic levels, dams showed decreased body weight gain and increased liver weight. Fetal effects included decreases in live fetuses, increased early and late resorptions and decreased fetal weight, along with an increase in fetuses/litters with malformations that included exencephaly and domed head, small or no eyes, clubbed paws, and various skeletal effects. It is also noted that benomyl, for which MBC is a major metabolite, also produced central nervous system (CNS) abnormalities in rat developmental studies. In the rabbit, increased resorptions, decreased implantations and reduced live litter sizes were observed at doses below maternally toxic levels. At maternally toxic levels, decreased maternal food consumption and weight loss during treatment were observed. Fetal effects included fused ribs and malformed cervical vertebrae, which may have been secondary to maternal stress. Although MBC is associated with developmental effects on the rat nervous system, no evidence of neurotoxicity has been observed in studies on adult animals.

MBC was most recently classified under the Agency 1986 cancer guidelines as a Group C, or "possible human carcinogen" based on the presence of hepatocellular adenoma and/or carcinoma in female CD-1 mice and aneugenic potential observed in genotoxicity studies. A cancer potency factor (Q_1*) of 2.39×10^{-3}(mg/kg/day)$^{-1}$ based on liver tumors in female mice is used to estimate cancer risk.

Endpoints selected for the most recent MBC human health risk assessment (2009) are shown in Attachment 2b. Non-dietary residential endpoints are required because antimicrobial uses may result in residential exposures. HED recommends re-evaluation of the endpoints for risk assessment during registration review, taking into consideration the results of new studies and current science policies at the time of the review.

It is noted that there is currently an additional 10x uncertainty factor (UF) for all endpoints due to the lack of data on developmental neurotoxicity and reproductive toxicity. An extended one-generation reproductive toxicity study is currently in progress to evaluate these effects. Uncertainty factors should also be re-evaluated during registration review, based on the findings and acceptability of this study.

Conclusions for Hazard Identification/Toxicology

Based on the recently revised pesticide data requirements (40 CFR Part 158), an immunotoxicity study (870.7800) is required. An extended one generation reproductive toxicity study, which includes additional measures of neurobehavioral parameters, is being conducted and may address uncertainties regarding reproductive toxicity and developmental neurotoxicity. Additionally, the Agency requested that the study include a cohort evaluating immunotoxicity of MBC, which could be used to satisfy the immunotoxicity study requirement.

During registration review, HED recommends reevaluation of the following points, taking into consideration the results of the additional studies received for MBC and ensuring consistency with science policies in effect at the time of review: (1) endpoints for risk assessment and (2) selection of the FQPA safety factor for relevant populations (i.e., infants and children).

Dietary Exposure

MBC is not registered for use on food in the US; therefore, no tolerances are established for its residues. However, dietary exposure to carbendazim residues can result from use of TM in food crops or from contamination of drinking water sources from the use of TM. Therefore, a dietary exposure assessment will be required.

In 2012, HED performed acute, chronic, and cancer dietary exposure assessments for carbendazim to determine the effect of the inclusion of residues in orange juice on the dietary risk estimates (D397646). These assessments were done because it was discovered that some shipments of imported oranges into the U.S. contained residues of carbendazim, although a tolerance was not established for residues in oranges. The analyses were based on the previous assessment of carbendazim exposure resulting from existing uses of TM. Two separate assessments were performed based on different sources of the drinking water concentrations. In the first assessment, EDWCs provided by EFED were used. These EDWCs were based on the use pattern for TM, and included two major turf scenarios and numerous crop scenarios. There were acute, chronic, and cancer risks of concern. However, when PDP monitoring data were used for residues in water, there were no acute, chronic, or cancer risks of concern. During registration review, HED and EFED will consider whether or not it is appropriate to use water monitoring data for dietary exposure assessment. At that time, a new dietary exposure assessment will be performed.

Conclusions for Dietary Exposure

HED anticipates performing a new dietary exposure assessment for carbendazim during registration review. The most current drinking water models will be used for this assessment. In addition, the most current version of the dietary model will be used, along with any potential changes in endpoints and doses for risk assessment

Residential Exposure

MBC provides effective protection against decay fungi, and has antimicrobial (i.e., microbiocide) and conventional uses. The MBC antimicrobial registered uses are formulated as in-can ready to use and dry-film preservatives in adhesives (non-food), caulks, concrete, grouts, inks, paints, paper (non-food), plastic, roof coatings, sealants, stains, and textiles. The MBC conventional use is for seasonal suppression of fungus for ornamental trees and is formulated as ready to use capsules. The products registered for use for tree injection are intended for use by professional applicators only, including arborists, so residential handler exposure is not expected for tree injection. MBC may be applied to ornamental trees in residential and non-residential landscapes, exterior plantscapes, and other areas where ornamental trees are grown; however, it is not for use on ornamental trees grown for sale. There is no residential post-application exposure expected for the tree injection use pattern.

MBC Handler Exposure

The primary source of information used to evaluate residential handler exposure and risk for use of MBC was the 2000 occupational and residential exposure assessment for MBC (D265419, 2000) and the 2009 residential exposure assessment for use in paint (D364554, 2009).

Paint Additives

At the time the 2005 RED risk assessment was completed, MBC was added to paints at a maximum concentration of 0.5 % ai (5 lbs ai/1000 lb paint) and to sealants at 1.5% (15 lbs ai/1000 lb sealant). In an effort to mitigate human health risks of concern for residential painters posed by MBC from this use, the RED required that label amendments be submitted to reduce the concentration of MBC in paint from 0.5% a.i. to 0.35% a.i. based on dermal MOEs which exceeded the Agency's level of concern (i.e., MOEs <1,000). In addition, the Agency required the registrant to conduct a dermal toxicity study with MBC. Since the 2002 RED, the most recent residential risk assessment for MBC was conducted for the purpose of completing an aggregate exposure and risk assessment associated with newly proposed uses of TM (D364554, 2009). HED re-assessed the use of MBC in paints, coatings, plasters, and sealants from the following application methods: brush, rollers, low-pressure hand wand and airless sprayers. The short-term handler dermal exposure was recalculated using the reduced 0.35% concentration of MBC and the new dermal point of departure (POD) of 20 mg/kg/day, selected from the dermal toxicity study. Because of the effects observed in the dermal study (testicular degeneration), and because the rat extended reproductive toxicity study had not yet been completed, HED concluded that an additional 10X FQPA factor should be retained as a database uncertainty factor (UF_{DB}) for all residential scenarios. Therefore, the LOC for risk assessment continued to be MOEs <1000. All dermal handler risk scenarios resulted in MOEs well below 1000 (MOEs ranging from 34 to 87) and were of concern. Short-term handler inhalation exposure scenarios were also recalculated using the oral NOAEL of 10 mg/kg/day and resulted in MOEs greater than 1000 and were not of concern. All residential handler cancer risk estimates associated with painting were below 3×10^{-6}.

Since the 2009 assessment, AD identified one label (EPA Reg # 365-80) that still has a concentration of MBC at 0.5 % a.i. and contacted the registrant who indicated that they will

reduce the rate to 0.35% a.i. AD anticipates the need to reassess residential handler paint use scenarios during registration review to ensure application rates are acceptable. In order to further refine exposure estimates, AD will require new exposure data for residential handlers applying paints and stains, as well as chemical specific product use information. The revised assessments will incorporate updated toxicological endpoints and new exposure data.

Tree Injections

The registered tree injection product labels state that they are intended for use by professional applicators including arborists. Therefore, a quantitative assessment for residential handler exposure resulting from the use of MBC for tree injection was not previously performed (G. Bangs, D265419, June 21, 2000). However, since these are not restricted use products, the "professional applicator" wording on registered labels is not considered enforceable, and HED assumes there is potential for homeowners to purchase and use these products. Currently, HED does not have unit exposure data to assess residential handler exposure associated with this use pattern. Furthermore, these products are formulated as ready to use and packaged in capsules which are inserted into a feed tube and dispensed into the tree. Therefore, the potential for handler exposure to MBC from tree injection is considered to be negligible. During registration review, no additional data or assessments are required for this use.

MBC Post-application Exposure

The primary source of information used to evaluate residential post-application exposure and risk for use of MBC was the 2000 occupational and residential exposure assessment for MBC (D265419, 2000) and the 2009 residential exposure assessment for use in paint (D364554, 2009).

Paint Additive

Post-application exposure (non-cancer and cancer) to MBC-treated paints, coatings, and sealants was anticipated to be only by the inhalation route, as the treated materials will have dried and will be relatively inert. It was anticipated that only very low exposures to MBC would be obtained from inhalation of vapors in a treated room; in addition to the calculated inhalation MOE of 30,000 for applying paint (2 gallons) with a brush, MBC has a very low vapor pressure (1.0×10^{-7} mmHg). However, a quantitative assessment of potential inhalation exposure was conducted by modeling the emission rate of the active ingredient from the product. The Multi-Chamber Concentration and Exposure Model (MCCEM) was used to estimate post-application inhalation exposures for occupants after painting one room (2 gallons of paint) in a home. The inhalation post-application risk estimates for toddlers and adults were MOEs of 1.1×10^6 and 4.6×10^6 respectively. The cancer risk estimate for adults was 3.6×10^{-10}.

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment for paint is not required due to MBC's low vapor pressure and low potential for aerosol generation. As a result, a post-application exposure assessment for paint vapors will not be required during registration review.

Plastic Toys and Textiles

Previous residential exposure assessments (D273465, 2001 and D364554, 2009) did not assess the new uses of plastic toys and textiles impregnated with MBC. Based on the use of MBC as a material preservative to treat textiles and plastics, there is potential for dermal and incidental oral exposure resulting from contact with treated clothing and toys made of plastic. During Registration Review, AD will conduct an exposure screening risk assessment using default assumptions (i.e., 100% and 5% transfer rates) for treated textiles using the most recent toxicological endpoints. If the residential risks are not of concern using the 100% default transfer rate assumption, residential post-application residue data for treated textiles will not be needed. However, if the risks are not acceptable, post-application residue data will be required. To support the Agency's assumption of a 5% transfer rate, an indoor surface residue dissipation study is required.

Tree Injection

A quantitative post-application exposure assessment has not been performed for the use of MBC tree injections to ornamental trees. However, the potential for post-application exposure is anticipated to be negligible due to the method of application, previously explained, the low application rate, and due to the tree tissue incorporation of the product thus preventing its release. No additional exposure assessments are anticipated during registration review for this use.

Conclusions for Residential Exposure

Additional residential exposure data are required for MBC. During registration review, AD will conduct a new residential handler exposure assessment that will incorporate any new toxicological endpoints, and methods or policies for estimating exposure risk estimates associated with the registered paints and stains products. In order to further refine exposure estimates, AD will require new handler exposure data for applying paints and stains (see data requirements, below) as well as chemical specific product use information. AD also anticipates the need to conduct a residential dermal and incidental oral post-application exposure assessment for plastic toys and textiles. In order to support the uses of MBC in textiles (e.g. clothes) and plastics (e.g. toys), AD will require a chemical-specific indoor surface residue dissipation study.

Aggregate Risk Assessment

The last aggregate risk assessment of MBC was conducted in 2002 for the TM RED, which examined MBC both as a degradate of TM and as an active ingredient. This assessment combined exposures to TM and MBC, considering total aggregate exposure from food, drinking water and residential sources of exposure from uses of both TM and MBC. In this assessment, risk estimates were conducted for exposure to TM and MBC from use of TM, and from all uses of TM and MBC combined. TM and MBC, along with other metabolites of concern, were added together for total risk estimates, based on both showing liver toxicity and developmental effects, and on simultaneous exposure to both compounds in a given food commodity. The acute aggregate risk was based on evaluation of diet + drinking water only and for uses of TM and

MBC combined exceeded the LOC for infants less than one year of age, but not other subpopulations. Short-term aggregate risk estimates were not conducted for TM and MBC from TM uses because the risks from MBC alone exceeded HED's level of concern. Specifically, HED identified risks of concern for residential painters. Chronic non-cancer aggregate exposure to all uses of TM and MBC exceeded the level of concern for infants and children 1-6 years of age. Aggregate cancer risk was 1.1×10^{-6} for combined TM and MBC from all food and residential uses.

For future aggregate risk assessments, the risks for TM and MBC will not be combined because although both compounds share a common target organ (liver), their overall toxicological profile differs. An updated aggregate risk assessment is anticipated during registration review that will take into account changes in endpoint selection and safety factors and scientific policies at the time of registration review.

Conclusions for Aggregate Exposure

A new aggregate risk assessment is anticipated during registration review that will reflect current scientific and exposure assessment policies. Additional toxicity studies received by the Agency may result in revised doses and endpoints and safety factors. The Agency will likely have to address acute, short-term and intermediate-term, chronic, and cancer risks for registration review.

Occupational Exposure

Handler Exposure

Registered MBC formulations include soluble concentrates/solid, emulsifiable concentrates, ready-to-use solutions, wettable powders and water dispersible granules. Products may be applied using a paint brush/roller, low pressure sprayer or airless sprayer, and ready-to-use tree injectors. The primary source of information used to evaluate occupational handler exposure and risk for use of MBC was the 2000 MBC occupational and residential exposure assessment and the 2001 assessment of TM/MBC for the RED (D265419, 2000 and D273465, 2001). All occupational handler scenarios for paint and stain products resulted in risk estimates greater than the LOC (LOC=MOEs equal to or greater than 100) at baseline (single layer clothing) and were not of concern, with one exception. The mixing/loading of wettable powders (0.5% a.i.) scenario resulted in an inhalation risk estimate of concern (MOE=8) at a baseline level of protection. In an effort to mitigate human health risks of concern posed by MBC, the RED required that label amendments should be submitted to reduce the concentration of MBC in paint from 0.5% a.i. to 0.35% a.i. based on dermal MOEs which exceeded the Agency's level of concern (i.e., MOEs <100). AD identified that one label (EPA Reg # 365-80) was still at 0.5 % a.i. and contacted the registrant who indicated that they will reduce the rate to 0.35% a.i. AD anticipates the need to reassess this scenario during registration review to determine whether or not the rates are acceptable with updated toxicological endpoints and exposure data.

As indicated previously in the residential section, a quantitative assessment for residential handler exposure resulting from the use of MBC for tree injection was not previously performed

(D265419, 2000). Currently, HED does not have unit exposure data to assess residential handler exposure associated with this use pattern. Furthermore, these products are formulated as ready to use and packaged in capsules which are inserted into a feed tube and dispensed into the tree. Therefore, the potential for occupational handler exposure to MBC from tree injection activities is negligible and no further data or assessments will be required for this use during registration review.

MBC Occupational Post-application Exposure

Dermal post-application occupational exposure to dried or "cured" paint containing MBC is not expected to be of concern. Handlers of MBC or MBC-treated materials are anticipated to have a greater exposure to MBC than any post-application occupationally-exposed group. Given the uncertainty and lack of information about post-application exposure to MBC, it is assumed that the handler risk estimates represent the high-end for possible post-application exposure. Post-application inhalation concerns are expected to be minimal based on the low MBC vapor pressure (1×10^{-7} mm Hg at 20° C) and the small amount of active ingredient in the ready-to-use product (maximum 3.5%). Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment is not expected for registration review.

The potential for post-application exposure resulting from tree injection of MBC is anticipated to be negligible due to the method of application, previously explained, the low application rate, and due to the tree tissue incorporation of the product thus preventing its release. No additional exposure assessments are anticipated during registration review for this use.

Conclusions for Occupational Exposure

During registration review, AD anticipates the need to conduct updated handler dermal and inhalation exposure risk assessments for the paint use with updated toxicological endpoints and updates to the Agency's standard assumptions for conducting handler exposure assessments, including revised unit exposure data. AD will also address whether any scenarios require additional PPE (i.e., gloves, dust mist respirator) or engineering controls (i.e., water soluble packets). Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for MBC, and is not expected for registration review.

Tolerance Assessment and International Harmonization

There are currently no food uses for MBC. See the tolerance harmonization discussion in the TM section of this document.

Data Requirements

The following studies are required for MBC:

Toxicology

870.7800 Immunotoxicity. This study is required *per* the revised pesticide registration data requirements (40 CFR Part 158, 2009). The Agency has previously discussed inclusion of a cohort in the rat extended one-generation reproductive toxicity study, currently in progress, evaluating immunotoxic parameters which may satisfy this guideline requirement.

Residue chemistry

There are no food uses for MBC. No new residue chemistry data requirements have been identified for MBC to support registration review.

Exposure

Occupational Handler

875.1200/875.1400 (Exposure Data):
- Occupational handler dermal and inhalation exposure applying paints/stains, slurries (airless sprayer, low pressure handwand and brush/roller);

875.1200/875.1400 (Exposure Data):
- Occupational dermal and inhalation for pouring liquid and or solid material preservatives formulations (paints/stains, slurries); and

875.1700 Product use information
- For occupational exposure assessments product use data are required for pouring liquid/solid material preservative formulation. The Agency needs to refine the daily amount handled for these procedures and a description of the pouring operations. The occupational data requirements may be conducted by the registrants or they may cite the completed or planned Antimicrobial Exposure Assessment Task Force (AEATF) studies.

Residential Handler

875.1200/875.1400 (Exposure Data):
- Residential handler dermal and inhalation exposure applying paint/stain (airless sprayer and brush/roller).

875.1700: Product Use Information:
- Product use for applying paints/stains
- Product use information for pouring liquid/solid material preservative formulation

Residential Post-application

875.2300: Indoor Residue Exposure Data
- Indoor surface residue dissipation data for plastic toys and textiles

875.2700: Product Use Information:

- For material preservative uses (plastic toys and textiles) in residential products

The residential exposure section indicates new residential risk assessments are anticipated for registration review. The need for additional exposure data was confirmed by the EPA's Scientific Advisory Board (SAP) in 1997. The residential data requirements may be conducted by the registrants or they may cite the completed or planned Antimicrobial Exposure Assessment Task Force (AEATF) studies.

CONSIDERATIONS FOR BOTH TM AND MBC

Public Health and Pesticide Epidemiology Data

For this evaluation, both the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredients TM and MBC (PC codes: 102001, 128872). The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to TM exposure. TM is not included in the AHS, and therefore this study does not provide information for this report.

OPP's IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6(a)(2) reports from registrants, other federal and state health and environmental agencies, and individual consumers. Since 1992, OPP has compiled these reports in IDS. The IDS contains reports from across the U.S., and most incidents have all relevant product information recorded. Reports submitted to the IDS represent anecdotal reports or allegations only, unless otherwise stated in the report.

IDS records incidents in one of two modules: Main IDS and Aggregate IDS:

> Main IDS contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics. This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one active ingredient (as opposed to pesticide products with multiple active ingredients) are considered to provide more certain information about the potential effects of exposure from the pesticide.
>
> Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries.

For the Main IDS, from January 1, 2008 to September 11, 2013, there were 5 incidents reported for single chemical only in the database. There were 3 additional incidents reported involving more than one chemical. One incident was classified as major severity (Table 1). The other incidents reported were classified as moderate severity.

In Aggregate IDS, from January 1, 2008 to September 11, 2013, there were 14 reported incidents involving TM and MBC. Overall, there are few incidents involving TM and MBC reported to IDS.

Table 1. Major Severity Incident Descriptions for TM

Human Incident		Chemical: TM			PC Codes: 102001, 128872	
Incident Package Report	Incident Date	Location	Reg Number	Product Name	Exposure Severity	Incident Description
020111 - 00270	1/1/2008	NC	000538-00088	LAWN FUNGUS CONTROL	Major	One individual chronically exposed in the home to a low level reported the following symptoms: tingling, numbness in feet, hands and toes, pain and progressing burning sensation in both arms and muscle twitches in legs. She also reported headaches and nausea. No one else in the family experienced any symptoms.

The SENSOR-Pesticides database covers 11 states from 1998-2009, although reporting varies from state to state. Cases of pesticide-related illnesses are ascertained from a variety of sources, including: reports from local Poison Control Centers, state Department of Labor workers' compensation claims when reported by physicians, reports from State Departments of Agriculture, and physician reports to state Departments of Health. Although both occupational and non-occupational incidents are included in the database, SENSOR-Pesticides is focused on occupational pesticide incidents, and is of particular value in providing that information. The state coordinator at each of the 11 respective state Departments of Health conducts case follow-up activities such as obtaining medical records to verify symptoms and severity. Using standardized protocol and case definitions derived from poison center reporting, the state SENSOR-Pesticide coordinator enters the incident information into the state-based system which is sent to NIOSH annually to be aggregated.

A query of SENSOR-Pesticides 1998-2009 finds 28 cases involving TM and MBC. Of these, nine cases involved a single active ingredient. Five of the nine cases were work-related. All nine cases were low in severity. Case symptoms are summarized in Table 2.

Table 2. SENSOR-Pesticides 1998-2009: Reported Health Effects for TM Cases	
Health Effect	# of Times Reported
Dermal	3
Ocular	0
Respiratory	2
Gastrointestinal	4
Renal	0
Nervous System	5
Cardiovascular	0
Miscellaneous	1
* Cases may report multiple health effects	

Based on the low frequency and severity of incident cases reported for both TM and MBC in both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time that would warrant further investigation. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

AD conducted a review of the incident data associated with antimicrobial use of MBC in OPP's Incident Data System (IDS) for the time period spanning 1997 to 2013. There were only 2 minor human incidents involving MBC reported in OPP's Incident Data System. Based on the low frequency and severity of incident cases, there does not appear to be a concern at this time that would warrant further investigation.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in the human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf). The OPP typically considers the highest potential exposures from the legal use of a pesticide when conducting human-health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who might be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

Cumulative Risk Assessments

TM and MBC are carbamates and members of the benzimidazole chemical group of fungicides, and is the pesticidally active moiety for TM. The Agency has not determined whether TM and

MBC and share a common mechanism of toxicity with other chemical substances. Prior to a final registration review decision for TM and MBC, the Agency will determine if there is any new information, such as new hazard or exposure data or information on changes to the use pattern, which would affect the need for a cumulative risk assessment. Should the Agency determine that new information on TM and MBC is available that could potentially trigger the need for a cumulative risk assessment and result in a risk of concern, the Agency will revisit the cumulative risk assessment.

Conclusions for Cumulative

A cumulative assessment is not needed at this time for TM and MBC, but may be required in the future if a cumulative assessment group (CAG) for benzimidazole fungicides is identified and the hazard or exposure data indicate that it is appropriate to include TM and MBC in that group.

For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Human Studies

Past TM and MBC risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. Many such studies, involving exposure to many different pesticides, comprise generic pesticide exposure databases such as the Pesticide Handlers Exposure Database (PHED) and the Agricultural Reentry Task Force (ARTF) Database. EPA has reviewed all the studies supporting these multi-pesticide generic exposure databases, and has found no clear and convincing evidence that the conduct of any of them was either fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. All applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied, and there is no regulatory barrier to continued reliance on these studies.

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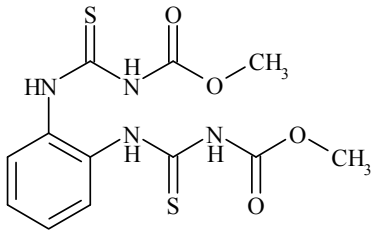
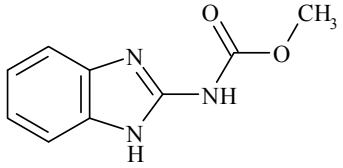
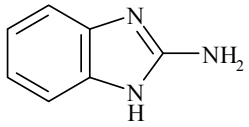
Attachments

Attachment 1. Chemical Identity Table for Thiophanate-methyl and Carbendazim
Attachment 2a. Thiophanate-methyl Endpoint Selection Tables
Attachment 2b. Carbendazim Endpoint Selection Tables
Attachment 3a. Summary of Acute, Subchronic and Chronic Toxicity Profile, Toxicological Doses for Thiophanate-methyl for Use in Human Health Risk Assessments.
Attachment 3b. Summary of Acute, Subchronic and Chronic Toxicity Profile, Toxicological Doses for Carbendazim for Use in Human Health Risk Assessments.
Attachment 4. International Residue Limit Status

Attachment 1. Chemical Identity Table for Thiophanate-Methyl and Carbendazim

Thiophanate-Methyl Nomenclature.	
Compound	
Common name	Thiophanate-methyl
IUPAC name	dimethyl 4,4′-(o-phenylene)bis(3-thioallophanate)
CAS name	dimethyl [(1,2-phenylene)bis(iminocarbonothioyl)]bis(carbamate)
CAS registry number	23564-05-8
End-use products	70% WP formulation (Topsin® M 70WP; EPA Reg. No. 73545-11); 4.5 lb/gal SC formulation (Topsin® 4.5FL; EPA Reg. No. 73545-13); 70% WP formulation (Topsin® M WSB; EPA Reg. No. 73545-16); 70% WDG formulation (Topsin® M 70 WDG; EPA Reg. No. 73545-18); 30% SC formulation (Tops® 30 Flowable Fungicide; EPA Reg. No. 264-990)
Regulated Metabolite	
Common name	MBC, carbendazim
CAS name	methyl 1H-benzimidazol-2-ylcarbamate
CAS registry number	10605-21-7
Metabolite to be included in risk assessment for plant commodities	
Common name	2-AB
Chemical name	2-aminobenzimidazole
CAS registry number	934-32-7

Attachment 2a. Summary of Toxicological Doses and Endpoints for Thiophanate-Methyl for Use in Human Health Risk Assessments

Table 2a.1. Summary of Toxicological Doses and Endpoints for Thiophanate-methyl for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49 years of age)	NOAEL= 20 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	aPAD =0.2 mg/kg/day	Developmental toxicity oral (gavage) study in the rabbit (1997 study) LOAEL = 40 mg/kg/day based on supernumerary ribs in fetuses and decreased fetal body weight
Acute Dietary (General population including infants and children)	An appropriate endpoint was not selected. This risk assessment is not required.			
Chronic Dietary (All Populations)	NOAEL= 8 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 3x	cPAD = 0.027 mg/kg/day	Chronic oral (one-year capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.
Incidental Oral Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL= 10 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 3x	Residential LOC for MOE = 300	Developmental toxicity oral (gavage) study in the rabbit (1997 study) LOAEL = 20 mg/kg/day based on decreased maternal body weight and food consumption.
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL= 100 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 3x	Residential LOC for MOE = 300	Twenty-one day dermal toxicity study in the rabbit LOAEL = 300 mg/kg/day based on decreased food consumption and body weight gain.
Dermal Long-Term (>6 months)	NOAEL=8 mg/kg/day. (dermal absorption rate = 7% relative to oral absorption)	UF_A= 10x UF_H=10x FQPA SF= 3x	Residential LOC for MOE = 300	Chronic oral (one-year capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.

Table 2a.1. Summary of Toxicological Doses and Endpoints for Thiophanate-methyl for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL=10 mg/kg/day (inhalation absorption rate = 100% relative to oral absorption)	UF_A= 10x UF_H=10x FQPA SF = 3x	Residential LOC for MOE = 300	Developmental toxicity oral (gavage) study in the rabbit (1997 study) LOAEL = 20 mg/kg/day based on decreased maternal body weight and food consumption.
Inhalation Long-Term (>6 months)	NOAEL= 8 mg/kg/day (inhalation absorption rate = 100% relative to oral absorption)	UF_A= 10 UF_H=10 FQPA SF = 3x	Residential LOC for MOE = 300	Chronic oral (one-year capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.
Cancer (oral, dermal, inhalation)	N/A	N/A	Q_1* = 0.0116 $(mg/kg/day)^{-1}$	78-week mouse dietary carcinogenicity study, based on increased incidence of liver adenoma/and/or carcinoma and/or hepatoblastoma combined tumor.

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 2a.2. Summary of Toxicological Doses and Endpoints for Thiophanate-methyl for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL=100 mg/kg/day	UF_A=10x UF_H=10x UF_{DB} = 3x	Occupational LOC for MOE = 300	Twenty-one day dermal toxicity study in the rabbit LOAEL = 300 mg/kg/day, based on decreased food consumption and body weight gain.

Table 2a.2. Summary of Toxicological Doses and Endpoints for Thiophanate-methyl for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Long-Term (>6 months)	NOAEL = 8 mg/kg/day (dermal absorption rate = 7% relative to oral absorption)	UF_A=10x UF_H=10x UF_{DB} = 3x	Occupational LOC for MOE = 300	Chronic oral (capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.
Inhalation Short- and Intermediate-Term (1-30 days)	NOAEL=10 mg/kg/day (inhalation absorption rate = 100% relative to oral absorption)	UF_A=10x UF_H=10x UF_{DB} = 3x	Occupational LOC for MOE = 300	Developmental toxicity oral (gavage) study in the rabbit (1997 study) LOAEL = 20 mg/kg/day based on decreased maternal body weight and food consumption.
Inhalation Long-term (1-6 months)	NOAEL=8 mg/kg/day (inhalation absorption rate = 100% relative to oral absorption)	UF_A=10x UF_H=10x UF_{DB} = 3x	Occupational LOC for MOE = 300	Chronic oral (capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.
Cancer (oral, dermal, inhalation)	N/A	N/A	Q_1* = 0.0116 $(mg/kg/day)^{-1}$	78-week mouse dietary carcinogenicity study, based on increased incidence of liver adenoma/and/or carcinoma and/or hepatoblastoma combined tumor.

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Attachment 2b. Summary of Toxicological Doses and Endpoints for Carbendazim for Use in Human Health Risk Assessments

Table 2b.1. Summary of Toxicological Doses and Endpoints for Carbendazim (MBC) for Use in Dietary and Non-Occupational (Residential) Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49 years of age)	Oral NOAEL= 10 mg/kg	UF_A= 10x UF_H=10x FQPA SF= 10x	aPAD =0.01 mg/kg	Developmental toxicity oral (gavage) study in the rat with MBC Developmental toxicity LOAEL = 20 mg/kg/day based on increases in skeletal variations and a possible threshold for malformations in fetuses and decreased fetal body weight.
Acute Dietary, General Population (including infants and children)	Oral LOAEL = 50 mg/kg (NOAEL not established)	UF_A= 10x UF_H=10x UF_L = 3x FQPA SF= 10x infants and children only	aPAD=0.017 mg/kg, infants and children; aPAD = 0.17 mg/kg, general population	Single dose rat study with MBC (Nakai *et al.* , 1992) LOAEL = 50 mg/kg based on adverse testicular effects including sloughing (premature release) of immature germ cells seminiferous tubules in one testicle, significant decrease in seminiferous tubule diameter and slight abnormal growth of the efferent ductules at 70 days post-exposure.
Chronic Dietary (All Populations)	Oral NOAEL= 2.5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF = 10x	cPAD = 0.025 mg/kg/day	2 year chronic oral toxicity study in the dog with MBC LOAEL = 12.5 mg/kg/day based on decreased body weight and food consumption.
Incidental Oral Short-Term (1-30 days)	Oral NOAEL= 10 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x	Residential LOC for MOE = 1000	Developmental toxicity oral (gavage) study in the rat with MBC Developmental toxicity LOAEL = 20 mg/kg/day based on increases in skeletal variations and a threshold for malformations in fetuses and decreased fetal body weight.
Incidental Oral Intermediate-Term (1-6 months)	NOAEL = 11 mg/kg/day (rounded to 10 mg/kg/day)	UF_A= 10x UF_H=10x FQPA SF= 10x	Residential LOC for MOE = 1000	90-day dog dietary study with MBC LOAEL = 35 mg/kg/day based on adverse liver effects.

Table 2b.1. Summary of Toxicological Doses and Endpoints for Carbendazim (MBC) for Use in Dietary and Non-Occupational (Residential) Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	Dermal NOAEL= 20 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x	Residential LOC for MOE = 1000	28-day dermal toxicity study in rats based on seminiferous tubule degeneration and hypospermia observed at the LOAEL of 120 mg/kg/day. (Note: results of this study have not yet been incorporated into an updated revised hazard characterization for MBC. A $BMDL_{10}$ has also been calculated)
Dermal Long-Term (>6 months)	Oral NOAEL=2.5 mg/kg/day. (dermal absorption rate = 3.5% relative to oral absorption)	UF_A= 10x UF_H=10x FQPA SF= 10x	Residential LOC for MOE = 1000	2 year chronic oral toxicity study in the dog with MBC LOAEL = 12.5 mg/kg/day based on decreased body weight and food consumption.
Inhalation Short-Term (1-30 days)	Oral NOAEL =10 mg/kg/day (assume 100% absorption relative to oral absorption)	UF_A= 10x UF_H=10x FQPA SF= 10x	Residential LOC for MOE = 1000	Developmental toxicity oral (gavage) study in the rat Developmental toxicity LOAEL = 20 mg/kg/day based on increases in skeletal variations and a possible threshold for malformations in fetuses and decreased fetal body weight.
Inhalation Intermediate- and Long-Term (1-6 months and > 6 months)	Inhalation NOAEL= 0.96 mg/kg/day (10 mg/m^3)	UF_A= 10x UF_H=10x FQPA SF= 10x,	Residential LOC for MOE = 1000	90-day rat inhalation study with benomyl LOAEL = 4.8 mg/kg/day (50 mg/ $m^{3)}$ based on olfactory degeneration in the nasal cavity.
Cancer (oral, dermal, inhalation)	N/A	N/A	Q1* = 2.39 x 10^{-3} $(mg/kg/day)^{-1}$	Two-year mouse dietary carcinogenicity study, based on increased incidence of hepatocellular (adenoma/and/or carcinoma) tumors.

The 10X FQPA factor was retained for all acute, short- and intermediate-term dietary and residential exposure scenarios (except general population acute dietary). The factor has been retained due to concern for potential neurodevelopmental toxicity raised by the observations of increased offspring sensitivity, CNS abnormalities from prenatal exposure and aneugenic potential. A 10X FQPA factor was not retained for chronic exposure because the windows of developmental sensitivity are not expected to be of chronic duration.

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key

date (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 2b.2. Toxicological Doses and Endpoints for MBC for Use in Occupational Human Health Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF* and Endpoint for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate Term (1-30 days and 1-6 months, respectively)	Oral NOAEL =10 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	LOC for MOE = 100 for occupational workers	Rat Developmental Study Developmental LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a possible threshold for malformations in fetuses of exposed dams
Dermal, Long-Term (>6 months)	Oral NOAEL =2.5 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	LOC for MOE = 100 for occupational workers	2 year dog study LOAEL= 12.5 mg/kg/day based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes of dogs.
Inhalation, Short-term (1-30 days)	Oral NOAEL =10 mg/kg/day (assume 100% absorption relative to oral absorption)	LOC for MOE = 100 for occupational workers	Rat Developmental Study Developmental LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a possible threshold for malformations in fetuses of exposed dams
Inhalation, Intermediate- and Long Term (1-6 months and >6 months)	Inhalation NOAEL= 0.96 (10 mg/m^3)	LOC for MOE = 100 for occupational workers	90 day rat inhalation study with benomyl LOAEL= 4.8 mg/kg/day (50 mg/m^3) based on olfactory degeneration in the nasal cavity.
Cancer	Q1* = $2.39x10^{-3}$ $(mg/kg/day)^{-1}$ (dermal absorption rate =3.5% relative to oral absorption; inhalation absorption rate=100% relative to oral absorption)	N/A	2 year mouse study based on hepatocellular (adenoma and/or carcinoma) tumors in female CD-1 mice

UF = Uncertainty Factor
LOC= Level of Concern
MOE = Margin of Exposure

Attachment 3a. Summary of Acute, Subchronic and Chronic Toxicity Profile, Toxicological Doses for Thiophanate-Methyl for Use in Human Health Risk Assessments.

Table 3a.1. Acute Toxicity Profile of Thiophanate-methyl (tech. a.i.)				
Guideline No.	**Study Type**	**MRID #**	**Results**	**Toxicity Category**
870.1100	Acute Oral, Rat	41644301	LD_{50} >5000 mg/kg, both sexes	IV
870.1200	Acute Dermal, Rabbit	41644302	LD_{50} >2000 mg/kg, both sexes	III
870.1300	Acute Inhalation, Rat	41482804	LC_{50} = 1.7 mg/L, males 1.9 mg/L, females	II
870.2400	Primary Eye Irritation, Rabbit	40095501	Slight ocular irritant	IV
870.2500	Primary Skin Irritation, Rabbit	40095502	Not a dermal irritant	IV
870.2600	Dermal Sensitization, Guinea Pig	41482805	Is a dermal sensitizer	N/A

N/A: Not applicable to this guideline study

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day dietary toxicity (rat)	42001701 (1990) Acceptable/guideline Males 0, 13.9, 155.0, 293.2, 426.9 or 564.7 mg/kg/day Females 0, 15.7, 173.4, 323.0, 478.8 or 647.3 mg/kg/day Tech., 96.55% a.i.	NOAEL = 15.7 mg/kg/day LOAEL = 155.0 mg/kg/day, based on anemia, increased serum cholesterol and calcium (males), increased liver and thyroid weights, increased kidney (males) weight and increased incidence of thyroid hyperplasia/hypertrophy, liver swelling and lipofuscin deposition, and glomerulonephrosis (males) were observed. At higher dose levels, effects included increased serum cholinesterase (males), increased thymus weight (females), increased incidence of glomerulonephritis (females) and fatty degeneration of the adrenal cortex were also reported.
870.3150	90-Day oral (capsule) toxicity (beagle dog)	41982203 (1992) Acceptable/guideline 0, 50, 200 or 800 mg/kg/day in gelatin capsules (HDT lowered to 400 on day 50 due to excessive toxicity) Tech., 96.55% a.i.	NOAEL < 50 mg/kg/day LOAEL (threshold) = 50 mg/kg/day, based on slight thyroid hypertrophy in 1 male and 1 female. At 200 mg/kg/day, thin/dehydrated appearance, tarry stools, decreased body weight/weight gain, decreased food consumption, slight anemia, increased serum cholesterol, decreased serum T3/T4 (females), increased liver and thyroid weights, thyroid follicular cell hypertrophy and hyperplasia, hypoplasia/atrophy of the prostate, thymic involution/atrophy (males) and depletion of spleen lymphoid cells were observed. At 800/400 mg/kg/day, mortality (1 male), increased platelet count were also observed.

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200	21/28-Day dermal toxicity (NZW rabbit)	42110801 (1991) Acceptable/guideline 0, 100, 300 or 1000 mg/kg/day, moistened with water (5 days/week, 6 hrs/day) Tech., 96.55% a.i.	Systemic toxicity NOAEL = 100 mg/kg/day Systemic toxicity LOAEL = 300 mg/kg/day, based on decreased food consumption in females. At 1000 mg/kg/day, consumption also decreased in males. Slight dermal irritation was observed at all dose levels.
870.3465	14-Day inhalation toxicity (rat)	42527601 (1992) Unacceptable/nonguide-line 0.0, 0.00514, 0.0151 or 0.247 mg/L Tech., 5.2% a.i. (Tops® 5 formulation)	NOAEL = 0.00514 mg/L LOAEL = 0.0151 mg/L, based on increased incidence of alveolar macrophages, pneumonocyte hyperplasia of the lung and nonsuppurative alveolitis. At 0.247 mg/L, decreased body weight gain (females) and increased incidence of lung microgranulomas (both sexes) were also observed.
870.3700a	Prenatal developmental in (rat)	00106090 (1981) Unacceptable/guideline (report lacking information on dosing solution analyses, maternal clinical sign and food consumption data, and individual litter data) 0, 100, 300 or 1000 mg/kg/day (gavage in 5% aq. gum arabic) tech., 97.2% a.i.	Maternal NOAEL = 300 mg/kg/day Maternal LOAEL = 1000 mg/kg/day, based on decreased body weight gain. Developmental NOAEL ≥1000 mg/kg/day Developmental LOAEL >1000 mg/kg/day
870.3700a	Prenatal developmental in (rat)	00146643 (1985) Acceptable/nonguideline 0, 18, 85, or 163 mg/kg/day (0, 250, 1200 or 2500 ppm in diet) tech., 95.3% a.i.	Maternal NOAEL = 18 mg/kg/day Maternal LOAEL = 85 mg/kg/day, based on decreased food consumption. Developmental NOAEL =163 mg/kg/day (HDT) Developmental LOAEL none established
870.3700b	Prenatal developmental in (NZW rabbit)	45051001 (1997) Acceptable/guideline 0, 5, 10, 20, or 40 mg/kg/day (gavage in 1% aq. methyl cellulose) tech., 97.28% a.i.	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = 20 mg/kg/day, based on decreased body weight gain and food consumption Developmental NOAEL= 20 mg/kg/day Developmental LOAEL = 40 mg/kg/day, based on increased supernumerary ribs and decreased fetal weight

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b	Prenatal developmental in (NZW rabbit)	40028801, 41056701 (1986) Unacceptable/nonguide-line 0, 2, 6 or 20 mg/kg/day (gavage in 1% aq. methyl cellulose) tech., 96.2% a.i.	Maternal NOAEL = 6 mg/kg/day Maternal LOAEL = 20 mg/kg/day, based on transiently decreased body weight gain, increased abortion/total litter loss Developmental NOAEL ≥20 mg/kg/day Developmental LOAEL = none
870.3800	Reproduction and fertility effects (rat)	42899101 to -05 (1993); 43624401 (1995) Acceptable/guideline Males 0, 13.7, 43.3 or 138.9 mg/kg/day; Females 0, 15.5, 54.0 or 172.0 mg/kg/day (in diet) tech., 95.9% a.i.	Parental systemic NOAEL <13.7 mg/kg/day Parental systemic LOAEL = 13.7 mg/kg/day, based on hepatocellular hypertrophy and thyroid hypertrophy/hyperplasia in males (females affected at mid and high dose). At ≥43.3 mg/kg/day, slightly decreased body weight gains in males and at 138.9 mg/kg/day, increased liver and thyroid weights (both sexes). Slight increase in TSH of P animals at Week 8. Reproductive NOAEL ≥ 138.9 mg/kg/day (HDT) Reproductive LOAEL > 138.9 mg/kg/day Offspring NOAEL = 13.7 mg/kg/day Offspring LOAEL = 43.3 mg/kg/day, based on slightly reduced body weights of the F2b offspring during lactation. Thyroid hypertrophy/hyperplasia seen at 138.9 mg/kg/day in males (F1 examined). Slight increase in TSH at Week 8 in F1 males.
870.3800	Reproduction and fertility effects (CD rat)	00117870 (1972) Unacceptable/guideline (upgradable with submission of test material purity) 0, 2, 8 or 32 mg/kg/day (estimated from ppm in diet) purity a.i. not stated	Parental systemic/reproductive NOAEL ≥32 mg/kg/day Parental systemic/reproductive LOAEL >32 mg/kg/day. Thyroid/liver not evaluated. Offspring NOAEL = 8 mg/kg/day Offspring LOAEL = 32 mg/kg/day, based on slightly decreased mean litter weights.
870.4100a	Chronic toxicity (rat)	See 870.4300	See 870.4300

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4100b	Chronic toxicity (beagle dog)	42311801 (1992) Acceptable/guideline 0, 8, 40 or 200 mg/kg/day in gelatin capsules Tech., 96.55% a.i.	NOAEL = 8 mg/kg/day LOAEL = 40 mg/kg/day, based on decreased body weight/weight gain, markedly increased serum TSH (1 male) and decreased T4 (males), increased serum cholesterol (males), increased abs/rel thyroid weights (both sexes) and thyroid follicular cell hypertrophy (females). At 200 mg/kg/day, tremors in all dogs 2-4 hrs postdosing (most on day 1; sporadically through day 17), slight anemia, increased serum alkaline phosphatase and cholesterol, increased relative liver weight, thyroid follicular cell hypertrophy in males and hyperplasia (both sexes) were also observed.
870.4200a	Carcinogenicity (rat)	See 870.4300	See 870.4300
870.4200b	Carcinogenicity (mouse)	42607701 (1992) Acceptable/guideline Males 0, 23.7, 98.6, 467.6 or 1078.8 mg/kg/day; Females 0, 28.7, 123.3, 557.9 or 1329.4 mg/kg/day Tech., 95.93% and 96.55% a.i.	Systemic toxicity NOAEL = 23.7 mg/kg/day Systemic toxicity LOAEL = 123.3 mg/kg/day, based on hepatocellular hypertrophy in females. At ≥98.6 mg/kg/day, decreased body weights,, sporadic effects on circulating T4 and TSH, increased thyroid and liver weights, increased heart weight (females), increased hepatocellular hypertrophy and increased atrial thrombosis were also observed. At the HDT, mortality was increased in both sexes. Increased incidence of hepatocellular adenomas in males at ≥467.6 mg/kg/day (control to high dose, 9%, 17%, 15%, 42% and 57%) and in females at ≥123.3 mg/kg/day (0%, 0%, 8%, 24% and 56%). Both sexes showed significant increasing trends and pair wise increases at the highest two dose levels.

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4300	Combined chronic toxicity/carcinogenicity (rat)	42896601 (1993) Acceptable/guideline Males 0, 3.3, 8.8, 54.4 or 280.6 Females 0, 3.8, 10.2, 63.5 or 334.7 Tech., 96.55% a.i.	NOAEL = 8.8 mg/kg/day LOAEL = 54.4 mg/kg/day, based on decreased body weight/weight gain (males; marginal in females), decreased food efficiency (males; marginal in females), sporadic effects on circulating T3/T4 and TSH, increased serum cholesterol and creatinine, decreased serum cholinesterase in females, increased liver, thyroid and kidney weights, liver hypertrophy and lipofuscin accumulation, thyroid hypertrophy and hyperplasia and lipofuscin accumulation in the kidney. At≥280.6 mg/kg/day, excessive mortality in males (2/50 survivors at termination), decreased body weight/weight gain in females, mild anemia, increased urinary protein, hyperparathyroidism (primarily in males), systemic calcification, increased severity of nephropathy and increased severity of liver and thyroid effects were also observed. The HDT was considered excessive in males. Increased incidence of thyroid follicular cell adenoma in males (control to high dose, 2%, 0%, 0%, 6% and 27%) and females (0%, 0%, 0%, 2% and 4%). Significantly increased trend in both sexes; pair wise incidence in males at high dose. Follicular cell carcinomas also observed in high dose males at high dose (11% vs. 0% all other doses; significant trend and pair wise comparison). Combined incidence significantly increased at high dose (2%, 0%, 0%, 6% and 32%) with positive increasing trend.
870.4300	Combined chronic toxicity/carcinogenicity (rat)	00017868 (1972) 0, 10, 40, 160 or 640 ppm (estimated at 0, 0.370, 1.54, 5.75 or 24.3 mg/kg/day, males and 0, 0.399, 1.62, 7.18 or 28.7 mg/kg/day, females) Unacceptable/guideline (not upgradable)	NOAEL = 5.75 mg/kg/day LOAEL = 24.3 mg/kg/day, based on decreased body weight/weight gain in males and females, increased thyroid epithelial cell columnar height, colloidal substance and hypertrophy in males and decreased spermatogenesis at termination in males. However, it was noted that testicular atrophy that was seen in some animals was not correlated with microscopic lesions to the testes. No evidence of carcinogenicity was observed but the overall number of surviving animals in the study was low.

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Gene Mutation 870.5100	Ames Assay (*S. typhimurium* and *E. coli* reverse gene mutation)	41608910 Acceptable/guideline 39.1 to 312.5 µg/plate without S9; 39.1 to 5000 µg/plate with S9	Not mutagenic with or without S9 activation in *S. typhimurium*
Gene Mutation 870.5100	Ames Assay (*S. Typhimurium* preincubation reverse gene mutation)	Published study (Zeiger *et al.* 1992, not submitted to Agency) Acceptable/nonguideline 0 to 10,000 µg/plate with or without rat or hamster liver S9. Tech., 95.1%	Weak equivocal response: 2-fold increases in revertant colonies of strains TA98 and TA100 at ≥3333.0µg/plate (precipitating concentration) with S9 and negative results in second assay. Negative response without S9.
Mammalian Cell *In Vitro* Cytogenetics 870.5375	*In Vitro* Mammalian Cell Cytogenetic Assay in Chinese Hamster Ovary (CHO Cells)	40980101 (1988) Acceptable/guideline 0 to 400 µg/ml culture medium without rat liver S9 and 0 to 1000 µg/mL with S9 Tech., 95% a.i.	Negative for structural chromosomal aberrations. Mitotic delay increased at 100 µg/ml without S9 and 335 µg/mL with S9. Cytotoxicity/compound insolubility observed at 400 µg/mL without S9 and 750 µg/ml with S9.
Mammalian Cell *In Vivo* Cytogenetics 870.5385	*In Vivo* Mouse Bone Marrow Micronucleus Assay	Published study (Barale, 1993, not submitted to Agency) Acceptable/nonguideline 1 mg/kg body weight, single gavage dose Tech., 95% a.i.	Borderline significant increase in polyploidy and hyperploidy. No increase in structural chromosomal aberrations.
Unscheduled DNA synthesis 870.5550	*In Vitro* Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes	40095503 (1981) Acceptable/guideline 0 to 1000 µg/mL culture medium tech., 99.8% a.i.	Negative for UDS induction at all doses tested. Cytotoxic at 1000 µg/mL.
Other Effects (no guideline number)	*In Vitro* Cell Transformation Assay in BALB/c 3T3 Cells	Published report (Perocco *et al.*, 1997; not submitted to the Agency) Acceptable/nonguideline 0 to 200 µg/mL culture medium with rat liver S9; 0 to 25 µg/mL without S9 Tech., 99.5% a.i.	Significant and reproducible increase in morphologically transformed foci at 25 µg/mL without S9 and ≥20 µg/ml with S9. Cytotoxicity observed at ≥25 µg/mL (pronounced at ≥50 µg/mL) without S9; only weak cytotoxicity with S9 (most pronounced at 100-200 µg/mL).

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.6200a	Acute neurotoxicity screening battery (Crl:CD(SD) rat)	48729901 (2005) Acceptable/guideline Initial study 0, 500, 1000 or 2000 mg/kg (gavage) Extension study 0, 50, 125, 500 or 2000 mg/kg (gavage)	NOAEL = not established (<50 mg/kg/day) LOAEL = 50 mg/kg/day (lowest dose tested) based on decreased landing foot splay in males and females on the day of dosing at all doses tested.
870.6200b	Subchronic neurotoxicity screening battery (Crl:CD(SD) rat)	48729902 (2005) Acceptable/guideline 0, 100, 500 or 2500 ppm Males 0, 6.2, 30.3 or 149.6 mg/kg/day; Females 0, 6.8, 34.9 or 166.3 mg/kg/day Tech., 99.7% a.i.	NOAEL = 30.3 mg/kg/day LOAEL = 149.6 mg/kg/day based on decreased body weight/weight gain and decreased food consumption in females and increased liver and thyroid weights (not examined microscopically).

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	42474802, 42601601 (1992) Acceptable/guideline low oral radiolabeled 14 mg/kg; repeated oral unlabeled 14 mg/kg for 14 days, followed by single radiolabeled; high oral radiolabeled 170 mg/kg Tech., 97.3%-98.5% radiochemical purity ^{14}C-thiophanate-methyl	Thiophanate-methyl was rapidly absorbed, metabolized and excreted at all dose levels (>90% within 24 hrs). Radioactivity did not accumulate in tissues (highest concentrations were in thyroid, 0.04-2.49 µg/g; liver, 0.17-2.15 µg/g; kidney 0.04-0.51 µg/g). Plasma half life for low, high and repeated doses was 2.8, 2.2 and 7.8 hrs, males and 2.5, 1.6 and 4.0 hrs, females. T_{max} was achieved at 1-2, 2-3 and 4-7 hrs at single low, repeated low and single high doses, respectively. The primary route of excretion was urinary following a single low oral dose (70-72% of administered radioactivity) but was fecal after repeated low (48-49%) or single high (67-70%) doses. Excretion in CO_2 was negligible. Metabolite profiles were qualitatively similar for all groups. Twelve identified and 4 unknown urinary metabolites were identified, including methyl 2-benzimidazolylcarbamate (MBC, 0.2 to 2.2% of recovered radioactivity) and other sulfate-conjugated and/or hydroxylated derivatives of the parent compound. The major urinary metabolite was 5-hydroxy(2-methoxycarbonylamino) benzimidazolyl sulfate (14-42%). Seven identified and 2 unknown fecal metabolites were identified; the major fecal metabolite was dimethyl[1,2-(4-hydroxyphenylene)]bis (iminocarbonothioyl)bis (carbamate) (3.5-11%). MBC was also identified in feces (0.5-2.7%). After a single low dose the parent compound was almost completely metabolized (1% of dose excreted), but it was the major excreted compound in feces of the repeated low dose (21-24%) and single high dose (52-56%) groups. No significant differences in metabolism were reported between males and females.

Table A.2.3: Special thyroid and liver mechanistic studies, supplement to chronic feeding/oncogenicity study in rats (MRID 42896601b; 1996-Acceptable/Non-guideline)			
Guideline	**Purpose of study**	**Doses**	**Results**
None	(1) Effect of short-term dietary administration of TM on liver and thyroid weights; circulating T3/T4 and TSH and serum cholesterol in male F344 rats	0 or 6000 ppm for 2 or 8 days Tech., 96.55% a.i. (all experiments in this study) Positive control groups: 500 ppm phenobarbital (liver enlargement) and 1000 ppm propylthiourea (PTU; antithyroid activity)	TM caused liver and thyroid enlargement; increased serum cholesterol and TSH; decreased T3 and T4 (decreases marginal at day 8). Phenobarbital (PB) caused liver enlargement and increased T3, T4, TSH and cholesterol at day 8. PTU caused thyroid and liver enlargement; increased TSH and cholesterol; decreased T3 and T4 (slight).
	(2) Reversibility of thyroid enlargement following termination of short-term dietary administration of TM in female F344 rats	0 or 6000 ppm for 8 days; half sacrificed on day 8 and half given basal diet for 8 additional days Positive (liver)/negative (thyroid) control group: 500 ppm Phenobarbital	Withdrawal of TM after 8 days' treatment caused reversal of the thyroid enlargement. Treatment with PB for 8 days' and subsequent withdrawal and recovery had no significant effect on thyroid weight.
	(3) Effect of T4 supplementation on thyroid and liver weights, TSH and serum cholesterol during short-term dietary administration of TM in male F344 rats	0 or 6000 ppm for 8 days; half of animals also received daily injections of 30 µg/kg L-thyroxine	Supplementation with T4 prevented thyroid enlargement and increased TSH but not liver enlargement or increased serum cholesterol.
	(4) Effect of TM on hepatic microsomal enzyme activities and protein concentration following short-term administration of TM to male F344 rats (livers collected from animals of study 1)	0 or 6000 ppm for 8 days Positive control: 500 ppm PB for 8 days	TM caused an increase in cytochromes p-450 and b5, and a pronounced increase in UDP-glucuronosyltransferase. Microsomal protein was also increased. PB caused an increase in cytochromes p-450 and b5, NADPH-cytochrome c reductase, UDP-glucuronosyltransferase and microsomal protein.
	(5) Effect of TM on porcine microsomal thyroid peroxidase activity	10^{-3} to 10^{-4}M, Guaiacol method Positive control: 10^{-4} to 10^{-6} PTU	The ED_{50} (effective dose to achieve 50% inhibition of thyroid peroxidase) for TM was 6 x 10^{-4}M and no inhibition was reported at 8 x 10^{-5} M (about 30-fold greater than PTU). The ED_{50} for PTU was 2 x 10^{-5}M and no inhibition was reported at 4 x 10^{-7}M.

Table A.2.3: Special thyroid and liver mechanistic studies, supplement to chronic feeding/oncogenicity study in rats (MRID 42896601b; 1996-Acceptable/Non-guideline)			
Guideline	**Purpose of study**	**Doses**	**Results**
	(6) Effect of TM on hepatocyte proliferation as measured by PCNA immunohistochemical staining following treatment with TM in male F344 rats and ICR mice	0 or 6000 ppm for 2 or 8 days Positive control: 500 ppm Phenobarbital	In mice, TM caused a sustained increase in PCNA staining and liver enlargement after 2 and 8 days' treatment. In rats, PCNA staining was increased at day 2 but not day 8; liver weights were increased at both times. In mice, PB caused increased PCNA staining at days 2 and 8 but less pronounced at day 8 than day 2. In rats, PCNA staining was increased at day 2 but not day 8. Liver weights were increased at both times.

Attachment 3b. Summary of Acute, Subchronic and Chronic Toxicity Profile, Toxicological Doses for Carbendazim for Use in Human Health Risk Assessments

Table 3a.1. Acute Toxicity of Carbendazim (purity as noted)

Guideline No.	Study Type	% a.i.	MRID	Results	Toxicity Category
870.1100	Acute Oral, Rat	98	00154508	LD_{50} >10,000 mg/kg	IV
870.1200	Acute Dermal, Rabbits	75	00154514, 00154515	LD_{50} >2,000 mg/kg	III
870.1300	Acute Inhalation, Rat	75	00154512, 00154513	LC_{50} >5 mg/L	III
870.2400	Primary Eye Irritation, Rabbit	>98	00154518	minimal to no irritation	III
870.2500	Primary Skin Irritation, Rabbit	75	00154516	slight irritation at 24 hr, normal by 72 hr	IV
870.2600	Dermal Sensitization, Guinea Pig	98	00154531	not a dermal sensitizer	N/A
870.6100a	Delayed neurotoxicity, hen	Not given	00154520	NOAEL = 2500 mg/kg	N/A

N/A Not applicable

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Carbendazim (MBC)

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3150	90-Day oral toxicity (dog)	00099130 (1970) Unacceptable/guideline 0, 100, 500 or 1500/2500 ppm in diet M: 0, 2.7, 14.4 or 40.7 mg/kg/day F: 0, 2.7, 11.3 or 35 mg/kg/day	NOAEL = 11.3 mg/kg/day (F); 14.4 mg/kg/day (M) LOAEL = 35 mg/kg/day (F), 40.7 mg/kg/day (M), based on histopathology changes in liver (1/4 males and 1/4 females) and testes (1/4 males) and increased alkaline phosphatase, cholesterol and SGPT. Liver effects included hepatic cirrhosis (hepatic cell necrosis, tubular collapse, and increased fibrous connective tissue around triads). Decreased testes weight in 3/4 males in the high dose. Note: The HDT group was gradually given increasing amounts of MBC using the following schedule: 500 ppm (3 days); 1000 ppm (2 days); 1500 ppm (2 days); 2500 ppm for a short time before the dose was lowered to 1500 ppm (week 3) due to decreased food consumption and weight loss.

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Carbendazim (MBC)			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200	28-Day dermal toxicity (rat)	47341601 (2007) Acceptable/guideline 0, 20, 120, 480 or 720 mg/kg/day	Systemic toxicity NOAEL = 20 mg/kg/day Systemic toxicity LOAEL = 120 mg/kg/day, based on seminiferous tubule degeneration and hypospermia. A $BMDL_{10}$ of 68 mg/kg/day was determined. Dermal irritation NOAEL ≥720 mg/kg/day Dermal irritation LOAEL > 720 mg/kg/day
870.3465	5-day inhalation toxicity (rat)	45849301 (2003) Acceptable/nonguideline 0, 0.17, 0.023 or 0.022 mg/L (4 hrs/day, 5 days) Second exposure group, 0, 0.058 or 0.178 mg/L (4 hr/day, 5 days) 97% carbendazim	NOAEL = 0.178 mg/L LOAEL = not determined (>0.178 mg/L)
870.3465	90-day inhalation toxicity (rat)	40399501 (1987) Acceptable/guideline 0, 0.01, 0.05 or 0.20 mg/L (4 hr/day, 5 days/week for 90 days) 95% benomyl (benomyl rapidly metabolizes to carbendazim *in vivo*)	NOAEL = 0.01 mg/L LOAEL = 0.05 mg/L, based on olfactory degeneration in the nasal cavity in males. At 0.20 mg/L, olfactory degeneration in females and decreased body weight and weight gain in males were also observed.
870.3700a	Prenatal developmental in (rat), oral	40438001 (1987) Acceptable/guideline 0, 5, 10, 20 or 90 mg/kg/day (GD 7-16) 98.8% carbendazim	Maternal NOAEL= 20 mg/kg/day, LOAEL = 90 mg/kg/day, based on increased absolute liver weight at 90 mg/kg/day Developmental NOAEL = 10 mg/kg/day LOAEL = 20 mg/kg/day, based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations at 20 mg/kg/day. At 90 mg/kg/day, increased malformations of the head, eyes, paws and skeleton were also seen.
870.3700b	Prenatal developmental in (rabbit)	00154466 (1985) Acceptable/guideline 0, 10, 20 or 125 mg/kg/day GD 7-19 98.7% carbendazim	Maternal NOAEL = 20 mg/kg/day LOAEL = 125 mg/kg/day based on increased abortions and decreased maternal body weight. Developmental NOAEL = 10 mg/kg/day LOAEL = 20 mg/kg/day based on decreased implantations and litter size, and increased resorptions. Malformations (fused ribs, malformed cervical vertebrae) were noted at 125 mg/kg/day. Deficiencies: Terminal maternal body weights were not corrected by using empty uterine weight instead of gravid weights.

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Carbendazim (MBC)			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (rat)	00088333 (1972) Unacceptable/guideline (not upgradable) 0, 100, 500, 5000 or 2500/10,000 ppm in diet 0, 5, 25, 250 or 125/500 mg/kg/day 50 or 70% carbendazim	NOAEL = 25 mg/kg/day LOAEL = 250 mg/kg/day based on decreased pup weight at weaning. Deficiencies: Litter (or fetal) weights were not measured at birth, therefore it is impossible to attribute weight decrease in 5000 and 2500/10000 ppm groups to prenatal or lactation period. Only 16 dams (20 dams for 5000 ppm), resulting in 10-16 litters per group were available, rather than the 20 litters recommended in the guideline. There was no special attention for the testes, a known target organ, including organ weights measurements. Note: 2500 ppm group increased to 7,500 ppm at week 18 and to 10,000 ppm at week 20 to end of study.
nonguideline	Single dose study (rat), gavage	Published study Acceptable/nonguideline Nakai *et al.* (1992) 0, 50, 100, 200, 400 or 800 mg/kg	NOAEL = not determined LOAEL = 50 mg/kg (lowest dose tested), based on premature release of immature germ cells two days post-exposure, and atrophy of a few seminiferous tubules and significant decrease in seminiferous tubule diameter 70 days' post-exposure.
870.4100a	Chronic toxicity (species)	See 870.4300	
870.4100b	Chronic toxicity (beagle dog) – two years, diet	00088333 (1972) Acceptable/guideline 0, 100, 500 and 1500/2500 ppm 0, 2.5, 12.5, or 37.5/62.5 mg/kg/day (doses adjusted for purity of a.i.) 53% a.i. carbendazim	NOAEL = 2.5 mg/kg/day LOAEL = 12.5 mg/kg/day, based on swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis and biochemical alterations indicative of liver damage (i.e., increased cholesterol, total protein, SGPT and alkaline phosphatase levels, and decreased A/G ratio). At 37.5/62.5 mg/kg/day, anorexia, distended abdomens and poor nutritional condition were reported.
870.4100b	Chronic toxicity, 1 year (beagle dog), diet	00164304 (1986) Acceptable/guideline 0, 100, 200, or 500 ppm in diet F:0, 2.93, 6.43 or 16.54 mg/kg M: 0, 3.2, 7.19, 17.07 98.8% carbendazim	NOAEL = 6.43 mg/kg/day (200 ppm) LOAEL: 16.54 mg/kg/day (500 ppm), based on possible transient increase in cholesterol (males and females) consistent with previous dog feeding studies.

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Carbendazim (MBC)			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200b	Carcinogenicity (mouse), oral	00154676, 0096513 (1982) Acceptable/guideline 0, 500, 1500 or 7500 (females) or 7500/3750 (males) ppm in diet 0, 75, 225, 1125 (females) or 1125/563 (males) mg/kg/day 99.3% a.i. carbendazim	NOAEL (non-cancer systemic) = 75 mg/kg/day LOAEL (non-cancer systemic) = 225mg/kg/day, based on liver toxicity (hepatocellular necrosis and swelling), body weight decrease and lymphoid depletion. In both sexes, there was an increased incidence of liver tumors. In males, hepatocellular carcinomas were noted at 225 mg/kg/day, while females exhibited carcinomas and adenomas at all dose levels. Note: The 7500 ppm was reduced to 3750 ppm at 66 weeks in males due to increased mortality.
870.4200b	Carcinogenicity (mouse), oral	00154679 (1982) Unacceptable/guideline 0, 50, 150, 300 or 1000/5000 ppm (diet) 0; 5.8-7.1; 17.1 -21.2; 34.4 - 41.9 or 522 – 648 mg/kg/day 99% a.i. carbendazim	NOAEL (non-cancer systemic) = 34.4 - 41.9 mg/kg/day LOAEL (non-cancer systemic) = 522 – 648 mg/kg/day, based on increases the incidences of hepatic cell hypertrophy, clear cell foci and hepatocellular necrosis. No increased incidence of carcinogenicity was noted. Note: The 1000 ppm dose was increased to 2000 ppm after 4 weeks and to 5000 ppm after an additional 4 weeks. Deficiencies: incomplete examination of most recommended tissues, blood and urine were not collected for analysis.
870.4200b	Carcinogenicity (mouse), oral	00153420 (1976) Unacceptable/guideline 0, 150, 300 or 5000 ppm (diet) 0, 22.5, 45 or 750 mg/kg/day 99% a.i. carbendazim	NOAEL = 45 mg/kg/day LOAEL = 750 mg/kg/day, based on hepatic alterations which included increased relative liver weights in both sexes, increased number of foci of cellular alterations in the liver in females, neoplastic nodules in females and hepatoblastomas in males Deficiencies: Brief methods, there were no historical data or microscopic or gross pathology reports for individual animals, and there was no assurance that the diets were analyzed for compound homogeneity and stability. In addition, there were no hematology or clinical chemistry analysis, nor urinalysis. Only organs or lesions suspected of being tumors and livers (2 sections) were examined histologically.

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Carbendazim (MBC)			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4300 (870.4100a and 870.4200a)	Chronic oral toxicity/carcinogenicity (rat)	00088333 (1972) and 00068982 (1978) Acceptable/guideline 0, 100, 500, 5000 or 2500/10000 (8557) ppm 0, 5, 25, 250 or 125/500 (430) mg/kg/day 53% a.i. carbendazim	NOAEL = 25 mg/kg/day LOAEL = 250 mg/kg/day, based on statistically significant decreases in red blood cell parameters (hematocrit, hemoglobin an red blood cells) in females and histological lesions in the liver (cholangiohepatitis and pericholangitis) in males and females. No evidence of carcinogenicity. Note: Dietary levels in 2,500 ppm were increased to 7,500 ppm at 18 weeks and to 10,000 ppm from weeks 20-104 for a time-weighted average of approximately 8557 ppm (430 mg/kg/day). Deficiencies: Only 36 rats/sex/dose tested (only 20 rats/sex were in 250 mg/kg/day dose group). Lack of complete clinical chemistry data and histopathology examination. At 24 months, only liver evaluated in 5 and 25 mg/kg/day groups and only liver, kidney and testes evaluated in 250 mg/kg/day group.
Gene Mutation 870.5265	Ames assay, *S. typhimurium* bacterial reverse gene mutation	Horst and Krahn (1980) Acceptable/guideline Up to 10,000 µg/plate	Positive: TA1537, TA98: Doses: 5000 and 10,000 µg/plate with S9; Negative TA1535, TA1538, TA100 at 100-10,000 µg/plate -/+S9 and all nonactivated doses with TA1537, TA98.
Gene Mutation 870.5265	Ames assay, *S. typhimurium* bacterial reverse gene mutation	00154668 (1983) Acceptable/guideline 100-5,000 µg/plate	Not mutagenic with or without S-9 activation in strains TA-1535, TA-97, TA-100, or TA-98
Gene Mutation 870.5265	Ames assay, *S. typhimurium* bacterial reverse gene mutation	00154669 (1983, 1986) Acceptable/guideline 100-5000 µg/plate	Not mutagenic with or without S-9 activation in strains TA-1535, TA-97, TA-100, or TA-98
Gene Mutation 870.5265	Ames assay, *S. typhimurium* bacterial reverse gene mutation	00154753 (1983) Acceptable/guideline 100-10,000 µg/plate	Not mutagenic with or without S-9 activation in strains TA-1535, TA-1537, TA-97, TA-100, or TA-98
Gene Mutation 870.5265	Ames assay, *S. typhimurium* and *E. coli* bacterial reverse gene mutation	43205504 (1992) Acceptable/guideline 5000 µg/plate	Not mutagenic with or without S-9 activation in strains TA-1535, TA-1537, TA-100, or TA-98; Negative for E. coli WP2 uvrA +/-S9
Gene Mutation 870.5265	*S. typhimurium* host mediated assay (mouse)	00154670 (1977) Acceptable/guideline 500 or 2000 mg/kg once daily for 2 days by gavage	Negative in ICR male mice administered 500 or 2000 mg/kg once daily for 2 days by oral gavage using strain S. typhimurium G46 (his -) as the indicator organism.

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Carbendazim (MBC)			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Gene Mutation 870.5265	Ames assay, *S. typhimurium* bacterial reverse gene mutation	00154670 (1977) Acceptable/guideline 10-3000 µg/plate without S9; 10-1000 µg/plate with S9; HID: 1000 µg/plate without S9; 3000 µg/plate with S9.	Negative TA1535, TA1537, TA1538, TA98, TA100; E. coli WP2 hcr +/-S9
Gene Mutation 870.5300	CHO/HGPRT forward gene mutation assay	00154671 (1980) Acceptable/guideline 3-628 µM (120 µg/mL) without S9; 3-654 µM (125 µg/mL) with S9 100% a.i.	Negative: Dose Range: 3-628 µM without S9 HID = 628 µM (120 µg/mL) without S9; Dose range with S9: 3-654 µM with S9 HID = 654 µM (125 µg/mL) with S9; ppt at ≥262 µM (50 µg/mL)+/-S9.
Gene Mutation 870.5300	Mouse lymphoma L5178y $TK^{+/-}$ Forward Gene Mutation Assay	00154673 (1980) Acceptable/guideline 5-50 µg/ml without S9; 2-25 µg/ml with S9 98% a.i.	Positive: (LED:50 µg/ml without S9); dose-dependent increases in mutation frequency over 8 concentrations of 12-25 µg/ml with S9. The response peaked at 25 µg/ml with S9, with a 7-fold increase in mutation frequency and 10% total growth. Colony sizing not performed. MBC was weakly mutagenic and two identified contaminants may be at least partially responsible for the mutagenic activity.
Gene Mutation 870.5300	Mouse lymphoma $TK^{+/-}$assay Forward Gene Mutation Assay	00159370 (1983) Acceptable/guideline 50-250 µM (about 10-50 µg/mL) without S9 25-250 µM (about 5-25 µg/mL) with S9	Negative at 50-250 µM (10-50 µg/mL) without S9. Positive at 75, 87.5, 100, 112.5, 125, 150, 200 and 250 µM with S9 but additional information sent by the registrant indicated that the mutagenicity was due to contaminants not to MBC.
Cytogenetics 870.5375	CHO chromosomal aberrations study	43205505 (1990) Acceptable/guideline 38-300 µg/mL	Negative with and without S9 activation up to a ppt and cytotoxic dose (≥300 µg/mL).
Mammalian bone marrow chromosomal aberrations 870.5385	*In vivo* mouse bone marrow micronucleus	41051510 (1976) Acceptable/guideline 500 mg/kg (ip) or 50, 100, 500 & 100 mg/kg/day once daily for 2 days by oral gavage.	Negative via ip; positive via oral gavage; dose-related increase in micronucleated polychromatic erythrocytes (MPEs) and micronucleated normochromatic erythrocytes (MNEs) at 100-1000 mg/kg-- no effect at 50 mg/kg but only sampled at 24 hours. MBC was a 2-5 times more potent inducer of micronuclei than benomyl.
DNA damage/repair, bacterial 870.5500	*B. subtilis* DNA damage/repair rec assay	00154670 (1977) Acceptable/guideline Up to 1000 µg/plate	Negative up to 1000 µg/plate without S9 *B. subtilis* H17, M45

Table 3a.2. Subchronic, Chronic and Other Toxicity Profile for Carbendazim (MBC)			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Unscheduled DNA synthesis 870.5550	*In vitro* unscheduled DNA synthesis in mice	00154754 (1981) Acceptable/guideline 0.0125-12.5µg/mL (highest effective dose, HID)	Not mutagenic for unscheduled DNA synthesis in primary mouse hepatocyte cultures.
Unscheduled DNA synthesis 870.5550	*In vitro* unscheduled DNA synthesis in rats	00154672 (1981) Acceptable/guideline 0.0125-12.5 µg/mL (highest effective dose, HID)	Not mutagenic for unscheduled DNA synthesis in primary mouse hepatocyte cultures.
Unscheduled DNA synthesis 870.5550	*In vitro* Unscheduled DNA synthesis assay in Human cells (explant from lung carcinomas)	43205506 (1992) Acceptable/guideline 0.3-300 µg/mL +/-S9	Negative up to a ppt (≥30 µg/mL) and cytotoxic doses (≥100 µg/mL).
In vitro sister chromatid exchange 870.5900	CHO cells in vitro sister chromatid exchange	40801201 (1988) Acceptable/guideline 0.4 to 40 µg/mL without activation; 5 to 40 µg/mL with activation >99% a.i.	Negative for SCEs in CHO cells at 0.4 to 40 µg/mL without activation, and at 5 to 40 µg/mL with rat liver metabolic activation. MBC induced a high degree of tetraploidy without activation (57-100%) at 1.33 to 40 µg/mL
Aneuploidy	*In vivo* bone marrow erythrocyte immunofluorescent antikinetochore micronucleus assay, BD-F1 mice	42911602 (1992) Acceptable/guideline 66, 1646 and 3293 mg/kg once by gavage	Positive at 1646 & 3293 mg/kg in females (48 hrs.) and 3293 mg/kg in males (48 hrs); 83-93% of micronuclei were kinetochore-positive at 3293 mg/kg; no effects at 1646 mg/kg (males) or 66 mg/kg (females).
870.7485	Metabolism and pharmacokinetics (rat)	41419201 (1990) Acceptable/guideline 50 or 1000 mg/kg single gavage dose; 50 mg/kg/day repeated oral dose 94% a.i. carbendazim	Carbendazim rapidly absorbed and extensively metabolized in CD/BR rats in all dose groups. Radioactivity excreted primarily via urine for low dose groups (54 to 66%) but at high dose only 41% was excreted in urine. Less than 1% retained in tissues (liver and carcass). Half life was about 12 hours, with 98% excreted by 72 hours postdosing. The primary routes of metabolism were oxidation of the phenyl ring, followed by conjugation to give sulfate and glucuronide conjugates of 5-hydroxycarbendazim and 5,6-dihydroxycarbendazim. Subsequent phenyl ring oxidation and N-oxidation at the imidazole nitrogen yielded 5,6-hydroxy-oxo-carbendazim N-oxide glucuronide conjugates, especially in females.

Attachment 4. Thiophanate-Methyl International Residue Limit Status

Thiophanate-methyl (102001; 11-4-2013)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex[2,3,4]
40 CFR 180.371 Plants: sum of thiophanate-methyl, dimethyl ((1,2-phenylene) bis (iminocarbonothioyl)) bis(carbamate), and its metabolite, methyl 2-benzimidazoyl carbamate (MBC), calculated as the stoichiometric equivalent of thiophanate-methyl		Carbendazim and Thiophanate-methyl methyl benzimidazol-2-ylcarbamate (carbendazim) and 1,2-di-(3-methoxy-carbonyl-2-thioureido)benzene, expressed as carbendazim		Sum of benomyl, carbendazim, and thiophanate-methyl expressed as carbendazim.
Commodity	Tolerance (ppm) /Maximum Residue Limit (mg/kg)			
	US	Canada	Mexico[1]	Codex[2,3,4]
Almond	0.1			
Almond, hulls	0.5			
Apple	2.0	5		3 pome fruits[3,4]
Apricot	15.0	5		
Banana	2.0			
Bean, dry, seed	0.2	1 beans		0.5 beans (dry) [4]
Bean, snap, succulent	2.0	1 beans		0.5 common bean (pods and/or other immature seeds) [4] 0.02 garden pea, shelled (succulent seeds) [4]
Beet, sugar, roots	0.2			0.1 sugar beet[4]
Cherry, sweet	20.0	5 cherries		10 cherries[4]
Cherry, tart	20.0	5 cherries		
Grain, aspirated fractions	12			
Grape	5.0	5		3[3, 4]
Onion, bulb	0.5			
Onion, green	3.0			
Peach	3.0	10		
Peanut	0.1			0.1[4]
Peanut, hay	5.0			3 peanut fodder[4]
Pear	3.0	5		3 pome fruits[3,4]

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex[2,3,4]
Pecan	0.1			
Pistachio	0.1			
Plum	0.5	5		
Potato	0.1	0.1		
Soybean, hulls	1.5			
Soybean, seed	0.2	1 beans		0.5 soya bean (dry) [4]
Strawberry	7.0	5		
Vegetable, cucurbit, group 9	1.0	0.5 cucumbers, melons. pumpkins, squash		0.5 squash summer[4]
Wheat, forage	1.1			
Wheat, grain	0.1			0.05[3, 4]
Wheat, hay	0.1			
Wheat, straw	0.1			
MRLs with NO US Equivalent				
Blackberries		6		
Boysenberries		6		
Carrot roots		5		
Citrus fruits		10		
Mushrooms		5		
Nectarines		10		
Pineapples		1		
Raspberries		6		
Tomatoes		2.5		
Berries and other small fruits (except grapes)				1 [3, 4]
Lettuce head				5[4]
Peppers chili				2[4]
Rye				0.1[3, 4]
Completed: M. Negussie; 11/08/2013				

[1] Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes.

[2] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.

[3] Based on data for carbendazim other than thiophanate-methyl.

[4] Based on data for thiophanate-methyl

(c) *Tolerances with regional registrations*. A tolerance with a regional registration is established for residues of thiophanate-methyl, dimethyl ((1,2-phenylene) bis(iminocarbonothioyl)) bis(carbamate), including its metabolites and degradates, in or on the commodity in the following table. Compliance with the tolerance level specified in this paragraph is to be determined by measuring only the sum of thiophanate-methyl, dimethyl ((1,2-phenylene) bis (iminocarbonothioyl)) bis(carbamate), and its metabolite, methyl 2-benzimidazoyl carbamate (MBC), calculated as the stoichiometric equivalent of thiophanate-methyl, in or on the commodity.

Commodity	Parts per million
Canola, seed	0.1